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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

4 Sawicky, H. H., M.D.; Bistrimate (sodium bismuth triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus. The Journal of Investigative Dermatology, vol. 9 #3 September 1947.

5 Howles, James K., M.D.; Treatment of Inflammatory-Dermatoses with Oral Bismuth (sodium bismuth triglycollamate). Southern Medical Journal, vol. 41 #11, pages 1033-1041, November 1948.

6 Pascher, Frances, M.D.; Sawicky, H. H., M.D.; Silverberg, M.G., M.D.; and Emmet, Richard, M.D.; Bistrimate for Lupus Erythematosus, Lichen Planus and other Dermatoses. Journal of Investigative Dermatology, vol. 10, #6, June 1948.

7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.

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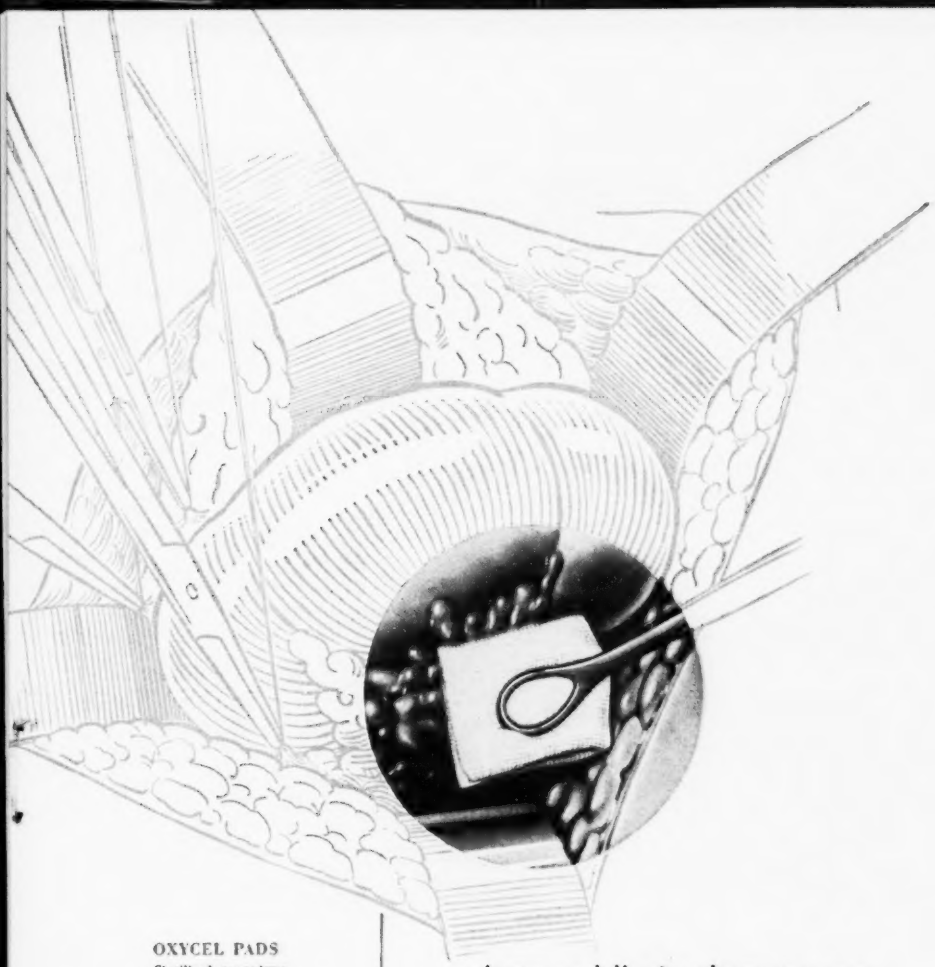

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1. **Gaul, L. E.,** "Overtreatment Dermatitis", J.A.M.A., 127:439-442, 1945
2. **Pillsbury, D. M.,** "Physiological Principles in the Management of Dermatitis", New Eng. J. Med., 244:423-429, 1951
3. **Underwood, G. B. and Gaul, L. E.,** "Overtreatment Dermatitis of the Feet," J.A.M.A., 130:249-256, 1946
4. **Miller, H. E., et al,** "Overtreatment in Dermatology", Calif. & West. Medicine, 51:251-253, 1939
5. **Lane, C. G.,** "Therapeutic Dermatitis", New Eng. J. Med., 246:77-81, 1952

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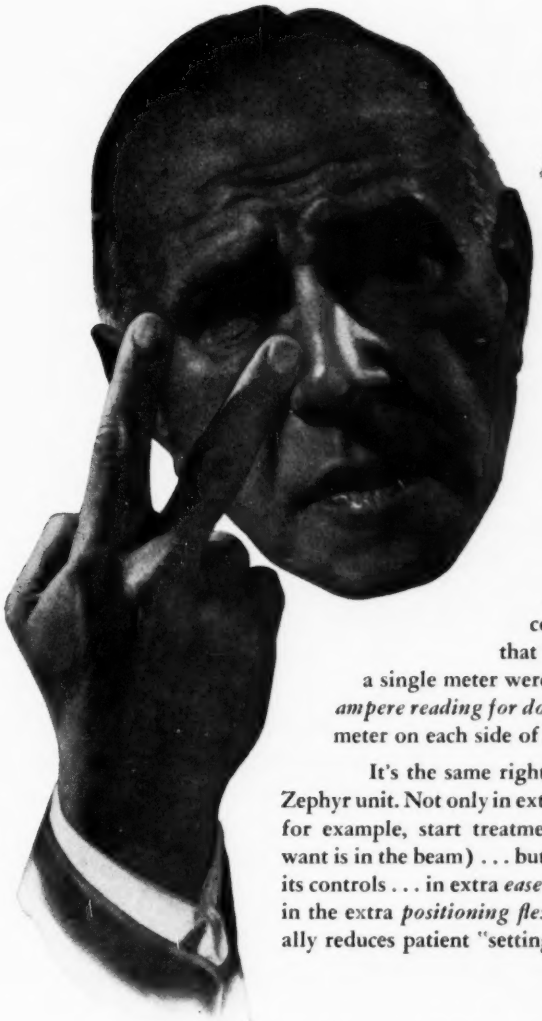

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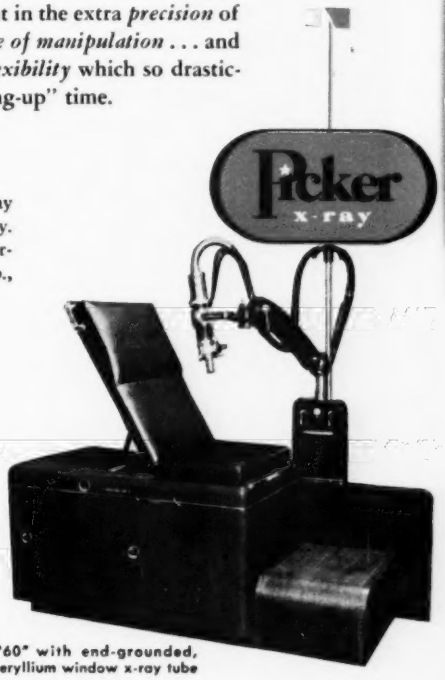

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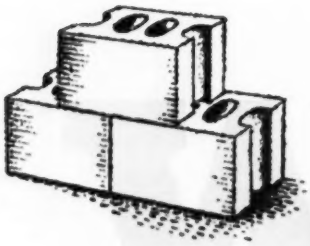

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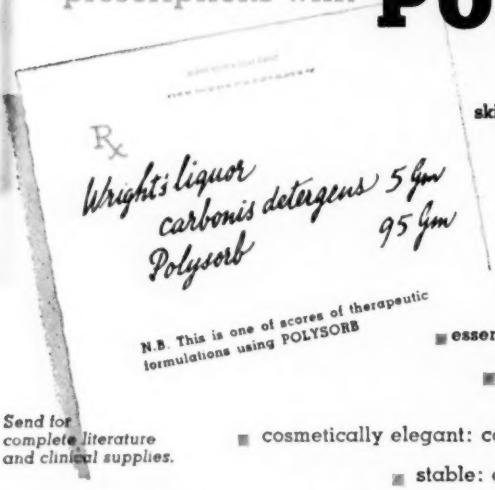
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SYMPOSIUM ON THE SWEAT APPARATUS

SOME HISTOPATHOLOGIC ASPECTS OF DISTURBANCES OF SWEATING

ARTHUR B. HYMAN, M.D.
NEW YORK

IN THE introductory article to the 1948 "Year Book of Dermatology and Syphilology," Sulzberger and Baer [1] stated that

> In modern studies it has been emphasized that anatomic and histopathologic morphologically discernible changes in the regions of sweat glands and pores merit equal or even closer attention than do functional changes or abnormalities of sweating.

Some of the earliest exploratory work related to the subject, which ranges from sudamina and miliaria rubra to thermogenic anhidrosis and tropical asthenia, was that of Robinson [2] in 1884. He found in sections of sudaminal skin that the vesicles were formed in the horny layer and that they were in direct communication with sweat ducts. The rete around the vesicles and the glands and ducts themselves were normal. The disease was, in his opinion, due to increase in the production of sweat, together with some obstruction to its escape caused ordinarily by detached and stretched epithelial cells. On the other hand, lesions of miliaria rubra were due to exudation of serum, corpuscles, and sweat into the rete mucosum around the orifices of the sweat ducts; and a "catarrhal" condition of the sweat glands was often seen. He concluded that miliaria was not an inflammatory disease of the sweat glands, but that it was a disorder of the skin around the duct orifices. That is to say, sudamina was a true obstructive "dyshidrosis," whereas miliaria was due to hyperhidrosis plus external irritation. Though Robinson was beginning to see the light and had partly realized the differentiation of this group of diseases from the mess heap of eczema, an analysis of his statements would indicate that they lack clarity.

The edifice of present-day dermatological thinking, which has been so carefully built by the painstaking and controlled work of O'Brien, Sulzberger, Herrmann, Shelley, Horvath, and Lobitz, to mention but a few of the investigators, had a solid foundation laid for it by Pollitzer,[3] who published his report in 1893. He found

---

This paper is the first in a Symposium on the Sweat Apparatus presented at the meeting of the Bronx Dermatological Society, Bronx, N. Y., Dec. 20, 1951.

From the Department of Dermatology and Syphilology of the Post-Graduate Medical School of New York University-Bellevue Medical Center, Dr. Marion B. Sulzberger, Chairman, and the Skin and Cancer Unit of the University Hospital.

1. Sulzberger, M. B., and Baer, R. L.: Eczematous Eruptions of the Hands, in Year Book of Dermatology and Syphilology, 1948, edited by M. B. Sulzberger, Chicago, The Year Book Publishers, Inc., 1949, pp. 23-27.

2. Robinson, A. R.: Miliaria and Sudamina, J. Cutan. Dis. **2**:362 (Dec.) 1884.

3. Pollitzer, S.: Prickly Heat, Lichen Tropicus, Miliaria Papulosa, Miliaria Rubra, etc., J. Cutan. & Genito-Urin. Dis. **11**:50-56 (Feb.) 1893.

that in prickly heat the cutis showed little change, apart from occasional widening of the coil gland lumens and a perivascular leucocytic infiltrate. The prickle cells were unaffected; the intercellular spaces were distended, and no exocytosis was seen. Here and there cyst-like dilatations of the sweat ducts, either of the uppermost or of the total intraepidermal portions were present. The contents were largely fluid, with varying numbers of epithelial and round cell elements and nuclear debris. When the vesicle was superficial, its floor was the stratum granulosum, and it was easily related to the sweat duct under it. When the whole thickness of the rete was involved, serial sections showed that the vesicle communicated with the sweat duct. The horny layer was lifted up by the vesicle fluid and was thickened on account of enlargement of the individual cells rather than from increase in cell number. The cells were often parakeratotic, especially in the vicinity of the duct orifices. Pollitzer clearly stated that the condition was not an eczema but was to be explained by a sudden outpouring of sweat, and was due to the formation of sweat retention "cysts" resulting from mechanical occlusion by the accumulation of swollen horn cells.

Subsequent work deals with developments from this essential histopathologic knowledge along four lines: (1) search for more exact information concerning all the sweat disturbances; (2) the experimental reproduction of these states, so that the underlying causes for the formation of the obstructive plugs are elucidated; (3) refinements in histopathologic and histochemical techniques, which though they, for the time being, give us only crumbs of information are of great importance for the dynamic understanding of sweat disturbances, once the basic, static morphology has been appreciated, and (4) the demonstration of the relation of histologically discernible and mechanically occlusive factors to other diseases.

1. DETAILS OF THE HISTOPATHOLOGY OF SWEAT-RETENTION DISTURBANCES

Relatively little attention had been paid to the problem of sweat disturbances from the time of Pollitzer's work until the matter became important in warfare. There are some notable exceptions, among them the experiments of Schlachta [4] published in 1908, which I shall deal with later. In 1944, Wolkin [5] and his associates sought the cause of thermogenic anhidrosis but, since they did no histologic studies and since they apparently knew nothing of sweat pore obstruction, they found no acceptable explanation. However, later in 1944 Allen and O'Brien [6] reported constant morphologic features in tropical anhidrosis of minute hyperkeratotic areas confined to and localized around the sweat ducts as a result of preceding miliaria rubra; the ostiums were occluded by keratin. Sweat was formed but was reabsorbed into the lymphatic system, with supression of sweating, rather than primary failure of secretion.

Sulzberger and Zimmerman's investigations [7] started with prickly heat. They found that semilunar plaques of hyperkeratosis and sometimes parakeratosis formed

4. Schlachta, J.: Über experimentelle Erzeugung der Miliaria crystallina, Monatsschr. prakt. Dermat. **46**:165 (Feb.) 1908.

5. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of Sweat Mechanism in the Desert, J. A. M. A. **124**:478-482 (Feb. 19) 1944.

6. Allen, S. D., and O'Brien, J. P.: Tropical Anhidrotic Asthenia, M. J. Australia **2**:335-336 (Sept. 23) 1944.

7. Sulzberger, M. B., and Zimmerman, H. M.: Studies in Prickly Heat: II. Experimental and Histologic Findings, J. Invest. Dermat. **7**:61-68 (Feb.) 1946.

covers over patent or dilated sweat duct orifices, or that the ducts were occluded by keratin plugs, paraductal lymphocytic reaction, intercellular edema and vesiculation of the epidermis in relation to the intraepidermal part of the duct, and edema of the corium around the duct. The walls of the ducts were invariably intact, even when adjacent lymphatics were distended, thereby suggesting absorption of sweat from ducts to lymphatics. The sweat glands and other accessory structures of the skin were unaltered.

The histologic features were fundamentally the same in tropical anhidrotic asthenia, which Sulzberger, Zimmerman, and Emerson [8] reported on later in the year. In this condition they sometimes saw subepidermal pools and hyperkeratotic and parakeratotic plugs floating on pools of fluid which had escaped from the ducts. After exercise, the sweat glands were distended, the periductal subepidermal pools were covered with thin epidermis, and the lymphatics around the ducts were dilated, but the subepidermal pools could always be traced to rupture of the ducts in or near the epidermis.

Working simultaneously, O'Brien [9] independently made closely similar observations in miliaria rubra and tropical anhidrosis. According to him, the basic pathogenesis is blockage of the sweat gland by closure of the keratin ring surrounding the duct orifices. As a result of dammed-back secretion, the distended sweat duct is ruptured just proximal to the keratin ring to produce a periductal vesicle. The vesicle is then obliterated by a newly formed plug of parakeratotic cells. Finally, in tropical anhidrosis, with full development of the plug, and because of the depth to which it extends, pressure of sweat leads to rupture of the obstructed duct at a deeper level—usually within the skin at the dermal-epidermal junction. Changes in the sweat glands are minimal; slight dilatation may be seen, but serious damage is prevented through relief of pressure by rupture. Similar changes in the pilosebaceous follicles, leading to blocking of secretion, result in folliculitis and acneform eruptions.

2. HISTOLOGY OF EXPERIMENTALLY REPRODUCED SWEAT-RETENTION LESIONS

Schlachta [4] reported from the Innsbruck Clinic in 1908 that he produced miliaria crystallina and anhidrosis by iontophoresis of various solutions at the site of an active anode (but not at that of an active cathode) and by spraying with ethyl chloride, if heat was applied later than three days after such treatment, but prior to desquamation, which took 5 to 13 days. Histologically there were produced superficial parakeratosis obliterating the sweat duct ostium, sweat retention, dilatation of the terminal part of the duct, and vesiculation.

Similar histologic studies on miliaria crystallina reproduced experimentally by iontophoresis, as well as by various other methods, were reported by Shelley and

8. Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K., Jr.: Tropical Anhidrotic Asthenia (Thermogenic Asthenia) and Its Relationship to Prickly Heat, J. Invest. Dermat. **7**:153-164 (Aug.) 1946.

9. O'Brien, J. P.: Study of Miliaria Rubra, Tropical Anhidrosis and Anhidrotic Asthenia, Brit. J. Dermat. **59**:125-158 (April-May) 1947.

Horvath [10] in 1949. They [11] furthermore reproduced miliaria rubra by a variety of modalities and found dilatation of the terminal part of the sweat duct, keratotic plugs, edema and lymphocytic infiltration immediately below in the cutis, and spongiosis and edema at the site of disorganized ducts to produce intraepidermal vesicles. The sweat glands and the ducts in the cutis were mostly normal.

Finally, Shelley [12] attempted to reproduce the vesicles of tropical anhidrosis by inducing sweating after injury to sweat pores by the "epilating" current. He found after destruction of the terminal part of the sweat duct either (*a*) a collection of fluid within a thickened stratum corneum and complete destruction of the epidermis and the upper dermal sweat duct at the point of entry of the needle, or (*b*) a vesicle in the necrotic epidermal area, or (*c*) a large keratotic plug overlying a subepidermal vesicle, the terminal sweat duct having been destroyed and the dermis showing lymphocytic infiltration.

It is impossible within the confines of this paper to do more than slight justice to O'Brien's 1951 article [13] on poral closure. In it he stresses what is for him of paramount importance, the bacterial (staphylococcal) factor in miliaria rubra and allied conditions, which he found in the disease states and which he was able to reproduce experimentally. He also demonstrated histologically the occlusive effects of excessive soaping and of kerosene applications.

In relation to O'Brien's discussion of the significance of poral closure and bacterial infection in tropical bullous impetigo, it is of interest that Tachau in his article [14] on pyodermas of sweat apparatus gave a detailed analysis of many possible etiological factors of eccrinal periporitis staphylogenes of infants but did not mention ostial plugging, though there were beautiful photographs showing substantial mechanical occlusion by keratin plugs.

Peck, Michelfelder, and Palitz [15] found that in adhesive-tape dermatitis there is keratotic plugging of the sweat duct ostiums, which, together with the macerating effect of the tape and bacterial multiplication, leads to lesions of miliaria rubra.

3. DATA DERIVED FROM REFINEMENTS IN HISTOLOGIC TECHNIQUES IN RELATION TO SWEAT APPARATUS

Sulzberger, Zak, and Herrmann [16] applied preparations containing aluminum sulfate to axillary skin. On biopsy they observed polymorphonuclear leucocytes and

10. Shelley, W. B.; Horvath, P. N.; Weidman, F. D., and Pillsbury, D. M.: Experimental Miliaria in Man: I. Production of Sweat Retention Anhidrosis and Vesicles by Means of Iontophoresis, J. Invest. Dermat. **11**:275-291 (Oct.) 1948. Shelley, W. B., and Horvath, P. N.: Experimental Miliaria in Man: II. Production of Sweat Retention Anhidrosis and Miliaria Crystallina by Various Kinds of Injury, ibid. **14**:9-20 (Jan.) 1950.

11. Shelley, W. B., and Horvath, P. N.: Experimental Miliaria in Man: III. Production of Miliaria Rubra (Prickly Heat), J. Invest. Dermat. **14**:193-204 (March) 1950.

12. Shelley, W. B.: Experimental Miliaria in Man: IV. Sweat Retention Vesicles Following Destruction of Terminal Sweat Duct, J. Invest. Dermat. **16**:53 (Jan.) 1951.

13. O'Brien, J. P.: The Etiology of Poral Closure, J. Invest. Dermat. **15**:95-152 (Aug.) 1950.

14. Tachau, P.: Schweissdrüsenpyodermien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1934, Vol. 9, Pt. 2, pp. 359-375.

15. Peck, S. M.; Michelfelder, T. J., and Palitz, L. L.: Further Studies on the Mechanism of Adhesive Tape Dermatitis, A. M. A. Arch. Dermat. & Syph. **63**:289-310 (March) 1951.

16. Sulzberger, M. B.; Zak, F. G., and Herrmann, F. J.: Studies of Sweating: II. On Mechanism of Action of Local Antiperspirants, Arch. Dermat. & Syph. **60**:404-418 (Sept.) 1949.

lymphocytes around and within the upper part of the eccrine ducts and similar perivascular inflammation in the upper cutis; some ducts and glands were dilated. But the apocrine glands showed expulsion of the nucleolus into the cytoplasm, karyolysis or pyknosis, and desquamation of lining cells to produce casts of the glands which might thus prevent outflow of secretion, but they saw no blocking of the ostiums. Such differentially selective changes suggest chemotaxis of the antiperspirant materials.

Sulzberger and colleagues [17] reproduced miliaria-rubra-like lesions experimentally by applying biologically electropositive agents, these being substances which result in a decrease of the outpouring of sweat. Vital staining with such dyes as thioflavine-S demonstrated the electronegativity of the spiral intraepidermal portions of the sweat ducts, which showed up as highly fluorescent with a filtered ultraviolet beam.

Pirilä and Eränkö [18] found that the nuclei and cytoplasm of the secreting cells of the sweat glands showed moderate to strong alkaline phosphatase activity. The basement membrane and the myoepithelium similarly showed a definite reaction. The proximal parts of the ducts were weakly stained; the distal portions were colorless. The sweat glands in atrophic skin tended to react less strongly than those in normal skin.

Eccrine and apocrine apparatus were investigated by Montagna, Chase, and Hamilton [19] for Schiff-reactive substances and lipids. They found that the eccrine secretory cells regularly showed abundant glycogen at their bases but little at the apices or in the lumens, where, however, there were masses of Schiff-reactive, diastase-resistant granules. Of eccrine duct cells only those not lining the lumens had a stippling of glycogen. Similarly in apocrine glands they found glycogen in the myoepithelium and at the bases of the "secreting" cells, but Schiff-reactive, diastase-resistant substances at the apices and in the lumens. The ducts showed glycogen in the basal cells, but not in the luminal ones. On staining with Sudan black both eccrine and apocrine glands showed coarse lipid globules at the apices of the secreting cells and fine stippling in the rest. The myoepithelium showed coarse sudanophilic droplets. The lipids were never anisotropic under polarized light.

Experimental work on cats by Sperling and Koppanyi [20] confirmed previous findings that blocking of the ducts does not prevent secretion. Such prevention can result only from inhibition of the secreting epithelium and the myoepithelial cells. The latter shrink during sweating and reexpand during anhidrosis, and thus apparently contribute fluid to the initial flow. These authors also showed that functional activity of sweat gland cells could be tested by staining with neutral leuco-methylene-

17. Sulzberger, M. B.; Herrmann, F.; Keller, R., and Pisha, B. V.: Studies of Sweating: III. Experimental Factors Influencing the Function of Sweat Ducts; Preliminary Report, J. Invest. Dermat. **14**:91-111 (Feb.) 1950.

18. Pirilä, V., and Eränkö, O.: Distribution of Histochemically Demonstrable Alkaline Phosphatase in Normal and Pathologic Human Skin, Acta path. et microbiol. scandinav. **27**:650-661 (April) 1950.

19. Montagna, W.; Chase, H. B., and Hamilton, J. B.: The Distribution of Glycogen and Lipids in Human Skin, J. Invest. Dermat. **17**:147-157 (Sept.) 1951.

20. Sperling, F., and Koppanyi, T.: Histophysiologic Studies on Sweating, Am. J. Anat. **84**:335-363 (May) 1949.

blue. In the presence of molecular oxygen this would stain inactive tissue blue, whereas actively secreting cells prevented the stain from changing from the leuco to the blue state.

These apparently isolated phenomena will one day surely be explained in relation to each other to reward us with a logical concatenation of all the fragments of knowledge we now possess.

4. HISTOLOGICALLY DISCERNIBLE SWEAT-RETENTION FACTORS IN OTHER DISEASES

Engelhardt and Melvin [21] reported a case of general acquired anhidrosis in a woman aged 49, in whom the only possibly significant etiological factor adduced was an attack of typhoid in childhood. Sections showed hyperkeratinization, but otherwise there was general atrophy of the epidermis. The sweat duct ostiums were plugged with keratin, and the sweat glands were moderately atrophic.

In cases simulating atopic dermatitis, in ichthyosis, atypical seborrheic dermatitis, and patchy prickly heat with papules, vesicles, and lichenification, Sulzberger, Herrmann, and Zak [22] speculated that essentially the same plugging of sweat ducts was at least the partial cause of the clinical states. In some, slit-like lumens were observed in the horny plugs of the sweat ducts. They found in cases of dermatitis following treatment with quinacrine (atabrine®) hydrochloride that the sweat glands showed various degrees of atrophy and dilatation and, in some instances, intraluminary epithelial proliferation. Short sections of sweat ducts could be found in some, but they were not connected to their glands, nor did they reach the surface, having become atrophied to leave behind strands of longitudinally arranged sheath cells.

Blom-Ides and Polano [23] reported on one patient in whom treatment with neoarsphenamine and bismuth was followed by a lichenoid eruption, and on another patient given neoarsphenamine therapy which was followed by exfoliative dermatitis. It was found that in summer these patients suffered severe symptoms of heat asthenia on exposure to sunlight or on exertion. The involved areas did not sweat, while normal skin did. A biopsy specimen from an involved area revealed atrophy of the epidermis and pronounced changes in the sweat glands, which showed no secretion. Attention was drawn to the similarity to Sulzberger's cases of tropical anhidrotic asthenia following quinacrine dermatitis.

Recently Lobitz and Kierland [24] reported on a patient with anhidrosis and generalized miliaria rubra, in whom examination showed no significant cause except subnormal absorption and utilization of vitamin A. The sweat duct ostiums were plugged; lymphocytic infiltrate was found in the periductal area, as well as around the sweat gland, though the latter itself was normal.

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21. Engelhardt, H. T., and Melvin, J. P. Jr.: General Acquired Anhidrosis, Am. J. M. Sc. **210**:323-328 (Sept.) 1945.

22. Sulzberger, M. B.; Herrmann, F., and Zak, F. G.: Studies of Sweating: I. Preliminary Report with Particular Emphasis on a Sweat Retention Syndrome, J. Invest. Dermat. **9**:221-242 (Nov.) 1947.

23. Blom-Ides, C., and Polano, M. K.: Infrequent Accessory Phenomena Occurring in Neoarsphenamine Dermatitis, Nederl. tijdschr. geneesk. **92**:3625-3629 (Nov. 6) 1948.

24. Lobitz, W. C., and Kierland, R. R.: Generalized Miliaria Rubra Associated with Abnormal Vitamin A Metabolism, A. M. A. Arch. Dermat. & Syph. **64**:411-416 (Oct.) 1951.

SUMMARY AND CONCLUSIONS

Mechanical occlusion of the eccrine ostiums is an essential histologic finding in sweat-retention disturbances.

Histologic features of the disease states are paralleled in the experimental reproduction of these conditions.

Histologic studies have had the following results:

1. "Antiperspirant" materials may have a selective action on apocrine gland cells.

2. The biologic electronegativity of the intraepidermal portion of the sweat duct has been demonstrated.

3. Differences between the alkaline phosphatase activity of different parts of the sweat apparatus have been demonstrated.

4. Differences between various parts of the eccrine apparatus, between various parts of the apocrine apparatus, and between various parts of certain cells of these structures, as to glycogen, Schiff-reactive, diastase-resistant material, and lipid content, have been demonstrated.

5. Participation of the myoepithelium in secretion has been demonstrated.

6. Functional activity of sweat apparatus cells can be tested.

Mechanical obstruction to the outpouring of sweat is a factor in the clinical status of a variety of diseases, including dermatitis following treatment with quinacrine (atabrine®) hydrochloride and dermatitides following the administration of neoarsphenamine with or without bismuth, and has also been found associated with disturbed vitamin A metabolism.

2 W. 87th St.

RECENT DEVELOPMENTS IN THE PHYSIOLOGY OF THE SWEAT APPARATUS

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THE RECENT developments in the physiology of sweating are numerous. Old concepts are strengthened, and new concepts are proposed. As in the past, many data are available on sweat gland function as it pertains to temperature regulation and acclimatization, to water and electrolyte balance, to nutrition and metabolism, and to functions of the vegetative nervous system.[1] In recent years more attention is being focused on the sweat apparatus as a secreting unit. Because of the time and the type of this discussion, I have chosen to limit the material of this presentation to the recent developments in regard to the functioning of the sweat apparatus itself.[2]

More evidence is available that cholinergic drugs can excite eccrine sweat glands when introduced locally by injection or by ion transfer.[3] Such sweating is produced in two ways—directly, by muscarine-like action, and reflexly, by nicotine-like action.[4] In addition to acetylcholine, other parasympathomimetic drugs will also produce sweating when applied locally. Those which act by inhibiting cholinesterase (neostigmine and physostigmine) will also enhance the action of acetylcholine in this regard.[3d] 2,4-Hexadien-1-ol applied topically to the skin produces local sweating by its muscarine-like effect on peripheral cholinergic receptors and, therefore, is free of toxic side-effects, since it produces no generalized parasympathetic

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1. List, C. F.: The Physiology of Sweating, Ann. Rev. Physiol. **10**:387, 1948.

2. Farber, E. M., and Lobitz, W. C., Jr.: The Physiology of the Skin, Ann. Rev. Physiol. **14**:519, 1952.

3. (*a*) Kadatz, R.: A Method for Investigating the Pharmacology of Human Sweat Glands, Arch. exper. Path. u. Pharmakol. **210**:159, 1950. (*b*) Kisin, E. E.: A Method of Pharmacological Study of the Sweating Function of the Skin in Situ, Vestnik venerol. i dermatol. **5**:27, 1948. (*c*) Gibson, T. E., and Shelley, W. B.: Sexual and Racial Differences in the Response of Sweat Glands to Acetylcholine and Pilocarpine, J. Invest. Dermat. **11**:137, 1948. (*d*) Janowitz, H. D., and Grossman, M. I.: The Response of the Sweat Glands to Some Locally Acting Agents in Human Subjects, ibid. **14**:453, 1950. (*e*) Issekutz, B., Jr.; Hentenyi, G., Jr., and Diosy, A.: Contributions to the Physiology of Sweat Secretion, Arch. internat. pharmacodyn. **83**:133, 1950. (*f*) Shelley, W. B., and Horvath, P. N.: Comparative Study on the Effect of Anticholinergic Compounds on Sweating, J. Invest. Dermat. **16**:267, 1951.

4. Coon, J. M., and Rothman, S.: The Sweat Response to Drugs with Nicotine-like Action, J. Pharmacol. & Exper. Therap. **73**:1, 1941.

stimulation.[5] It is interesting that there are sexual and racial differences in sweat gland responses to acetylcholine; the male is more responsive than the female and the Negro more so than the white.[6]

Although anticholinergic drugs given orally (atropine, etc.) can significantly reduce sweating, evidence is presented [3f] that it is futile to attempt to produce complete anhidrosis in this manner. The anhidrotic effect can be achieved only by the use of large doses, and even then for only a short time. However, if such drugs as scopolamine or atropine are topically applied to the skin by iontophoresis, the local thermal sweating can be markedly inhibited for days. Such a procedure might be valuable from the therapeutic as well as the experimental standpoint.

Although sweating has always been regarded as a cholinergic (i. e., parasympathetic) function, recently the question has been raised of the existence of an adrenergic (i. e., sympathetic) component in the nervous mechanism of human sweat glands.[7] Epinephrine, arterenol (norepinephrine), and phenylephrine (neo-synephrine®) induced moderate sweating when injected intravenously or intradermally. An adrenergic blocking agent, such as dibenamine® (dibenzyl betachlorethylamine hydrochloride) can block this effect (and block spontaneous palmar sweating); an anticholinergic drug, such as atropine, could not alter the adrenergic response. The sweat gland response to epinephrine is greatest in both sexes at about 14 years of age (being least in the child under 12 years and in the adult over 62). Interestingly, the sweat glands of the one-week-old newborn had the same excitability to epinephrine as those of the puerperal mother. Although there seems to be no doubt that the sweat glands respond directly to epinephrine, it is felt that the existence and function of an adrenergic (i. e., sympathetic) innervation of human eccrine sweat glands are not yet proved (cf. Haimovici [7b] and Sonnenschein and associates [8]).

The manner and rate in which the sweat is discharged from the secreting unit are becoming better understood.[9] Sweat glands do not act continuously except under extreme excitation. There is a periodicity or pulsatility to sweat secretions. At low sweat rates, the pulses appear in bursts; at moderate rates, they occur continuously with an average frequency of six to seven per minute; at very high evaporative levels, both the frequency and amplitude of the pulsations are dampened.

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5. Janowitz and Grossman.[3d] Koppanyi, T.: Hexadienol, a Locally-Acting Diaphoretic and a New Diagnostic Agent, J. Am. Pharm. A. (Scient. Ed.) **34**:221, 1945.

6. Footnote *3d* and *f*. Kahn, D., and Rothman, S.: Sweat Response to Acetylcholine, J. Invest. Dermat. **5**:431, 1942.

7. (*a*) Kisin.[3b] Haimovici, H.: (*b*) Evidence for an Adrenergic Component in the Nervous Mechanism of Sweating in Man, Proc. Soc. Exper. Biol. & Med. **68**:40, 1948; (*c*) Evidence for Adrenergic Sweating in Man, J. Appl. Physiol. **3**:573, 1951. (*d*) Sonnenschein, R. R.: Local Sweating in Man Induced by Intradermal Epinephrine, Proc. Soc. Exper. Biol. & Med. **71**:654, 1949. (*e*) Wada, M.: Sudorific Action of Adrenalin on the Human Sweat Glands and Determination of Their Excitability, Science **111**:376, 1950.

8. Sonnenschein, R. R.; Kobrin, H.; Janowitz, H. D., and Grossman, M. I.: Stimulation and Inhibition of Human Sweat Glands by Intradermal Sympathomimetic Agents, J. Appl. Physiol. **3**:573, 1951.

9. Albert, R. E., and Palmes, E. D.: Pulsatile Evaporative Rates from Small Skin Areas as Measured by an Infra-Red Gas Analyzer, Federation Proc. **8**:1, 1949. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: II. Chloride, Arch. Dermat. & Syph. **56**:462, 1947.

In a given area of the skin there are noted peaks and depressions in the number of functioning thermal-regulating sweat glands.[10] The preliminary response to mild exercise is an increasing number of functioning glands; as the stimulus to sweating becomes even stronger, there is an increased output of individual glands. Such periodicity and number of participating glands vary depending upon the outside temperature, peripheral stimulation, and the emotional state of the individual. This and other evidence suggest the presence of a bilaterally and periodically discharging sudomotor center, since thermoregulatory sweating may be elicited in two different ways: 1. The sudomotor centers may be directly stimulated by overheated blood reaching them. 2. The centers may also be indirectly activated by means of reflexes from cutaneous and visceral impulses.

The average output of a "typical" sweat gland has been calculated to be about 0.003 mg. per minute (those on the dorsum of the hand secreting about one-half the amount that those on the arms and legs do).[10d]

Sulzberger and colleagues[11] have submitted the hypothesis that electronegativity of the distal end of the sweat duct maintains an electrophysiologic potential along the ducts which facilitates and expedites the movement of sweat toward the skin surface by electro-osmosis.

Thermal sweating, as a rule, starts in nude subjects when the skin temperature exceeds 94 F. Though thermal-regulating sweating is generalized, there are marked differences in sweating rates on different skin regions. Thermal sweating is greatest on the trunk, diminishing, in order of amount, on the head and on the extremities.[12]

The chemical and physiological histology of the secreting sweat unit has also been under scrutiny in animals and man.[13] Prolonged secretory activity of the sweat gland in man leads to complete disappearance of glycogen from the acinar cells.[13c] The question is raised whether this glycogen is a precursor of lactic acid in the sweat.[14] Fats, sulfhydryl groups, desoxyribonucleic acid, and alkaline and acid phosphatase, which are also present in the cells, are unaffected by secretory activity.[13c]

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10. Randall, W. C.: (*a*) Quantitation and Regional Distribution of Sweat Glands in Man, J. Clin. Invest. **25**:761, 1946; (*b*) Sweat Gland Activity and Changing Patterns of Sweat Secretions on the Skin Surface, Am. J. Physiol. **147**:391, 1946. Randall, W. C., and McClure, W.: (*c*) Quantitation of the Output of the Sweat Glands and Their Response to Normal Stimulation, ibid. **155**:462, 1948; (*d*) Quantitation of Output of Individual Sweat Glands and Their Response to Stimulation, J. Appl. Physiol. **2**:72, 1949.

11. Sulzberger, M. B.; Herrmann, F.; Keller, R., and Pisha, B. W.: Studies of Sweating: III. Experimental Factors Influencing the Function of the Sweat Ducts, J. Invest. Dermat. **14**:91, 1950.

12. McArdle, B., cited by List.[1] Sodeman, W. A., and Burch, G. E.: Regional Variations in Water Loss from the Skin of Diseased Subjects Living in a Subtropical Climate, J. Clin. Invest. **23**:37, 1944. Burch, G. E.: Environmental Conditions Which Initiate Sweating in Resting Man, Proc. Soc. Exper. Biol. & Med. **67**:521, 1948. Weiner, J. S.: Regional Distribution of Sweating, J. Physiol. **104**:32, 1945.

13. (*a*) Bunting, H.; Wislocki, G. B., and Dempsey, E. W.: The Chemical Histology of Human Eccrine and Apocrine Sweat Glands, Anat. Record **100**:61, 1948. (*b*) Sperling, F., and Koppanyi, T.: Histophysiologic Studies on Sweating, Am. J. Anat. **84**:355, 1949. (*c*) Shelley, W. B., and Mescon, H.: Histochemistry of the Human Eccrine Sweat Gland, J. Invest. Dermat., to be published.

14. Weiner, J. S., and Heyningen, R.: Lactic Acid and Sweat Gland Function, Nature, London **164**:351, 1949.

When "tolerance" type studies [15] were carried out on palmar sweat with glucose, urea, uric acid, creatinine, ammonia, nitrogen, and chloride, the sweat apparatus was found (1) to bar glucose effectively from reaching the surface of the skin, even though the levels in the blood were elevated acutely and chronically; (2) always to concentrate urea in the sweat above the level (high or low) of urea in the blood; (3) to hold the creatinine and uric acid levels in the sweat below those in the blood (when the blood levels are elevated, creatinine is secreted quickly but uric acid reluctantly), and (4) to produce ammonia nitrogen and also to concentrate chlorides. These results suggest that the coil (acinar) portion of the gland acts as a selective secretor and that the duct and/or coil reabsorbs water from the sweat.

It has also been shown [16] that the concentration of sodium in the sweat varies in parallel with the rate of flow when the gland is stimulated by a cholinergic drug, but that the concentration of urea in the sweat is independent of this rate of flow.

The interpretation of electrolyte concentrations in sweat is once again under discussion. Earlier reports correlated the chloride concentration of sweat with sweating rates, skin temperatures, acclimatization, etc. Recently Conn and his associates [17] pointed to the probability that the sweat electrolyte pattern can be used in clinical and experimental medicine as an indication of either diminished or excessive adrenal production of "salt-active" corticosteroids. The complicated process of metabolic acclimatization to heat was thought to be accomplished by increased secretory activity of adrenal cortices which in turn, have been activated by corticotropin (pituitary adrenocorticotropin). The studies of Locke and co-workers [18] also suggested that the chief determinant of their "sweat-chloride-rate index" values is an adrenal cortex hormone which acts chiefly upon electrolyte and water metabolism. However, they also showed that, under conditions of a constant hormonal status, sweat electrolyte composition is influenced by nonendocrine factors related to thermal stimulus, skin temperature, and rate of sweating.

It seems unfair not to include so many other excellent studies on the physiology of sweating, the technique of such studies, and the additional work on the abnormal functioning of the sweat apparatus. However, this discussion had to be limited in its extent. Since it is the clinical dermatologist who has especial interest in the physiology of the sweat apparatus itself, particularly as it pertains to the functions of the skin, I have selected some material which can be of value to us as clinicians in the practice of our specialty.

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15. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: III. Reducing Substances (Glucose), Arch. Dermat. & Syph. **56**:819, 1947; IV. Urea, ibid. **56**:827, 1947. Lobitz, W. C., Jr., and Mason, H. L.: Chemistry of Palmar Sweat: V. Ammonia Nitrogen, ibid. **57**:69, 1948; VI. Uric Acid, ibid. **57**:387, 1948; VII. Discussion of Studies on Chloride, Urea, Glucose, Uric Acid, Ammonia Nitrogen, and Creatinine, ibid. **57**:907, 1948.

16. Dole, V. P.; Stall, B. G., and Schwartz, I. L.: Methods for Local Induction and Quantitative Analysis of Human Sweat, Proc. Soc. Exper. Biol. & Med. **77**:412, 1951.

17. Conn, J. W.; Louis, L. H.; Johnson, M. W., and Johnson, B. J.: Electrolyte Content of Thermal Sweat as an Index of Adrenal Cortical Function, J. Clin. Invest. **27**:529, 1948. Conn, J. W.: Electrolyte Composition of Sweat: Clinical Implications as an Index of Adrenal Cortical Function, Arch. Int. Med. **83**:416, 1949; Production of Endogenous "Salt-Active" Corticoids as Reflected in Concentrations of Sodium and Chloride of Thermal Sweat, J. Clin. Endocrinol. **10**:12, 1950.

18. Locke, W.; Talbot, N. B.; Jones, H. S., and Worcester, J.: Studies on the Combined Use of Measurement of Sweat Electrolyte Composition and Rate of Sweating, J. Clin. Invest. **30**:325, 1951.

METHODS OF EXPLORING HUMAN APOCRINE SWEAT GLAND PHYSIOLOGY

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FOR CENTURIES it has been known that there are large, grossly visible sweat glands in the axillae of man. It has been known almost as long that these large sweat glands produce an odoriferous secretion of variable color. Through the years, anatomists learned that these glands are not limited to the axillary region. They are present in the mammary region, in the pubic area, around the umbilicus, on the labia, and about the anus. Moreover, they are seen in modified forms in the eyelid (glands of Moll) and in the external auditory canal ("wax glands"). Comparative histologic studies revealed that the apocrine sweat gland is found in all mammals. Early histologic investigations indicated that the apocrine secretion was a unique type, in that in addition to the secretion of fluid there was a "decapitation" of secretory cells. This cellular secretion manifests itself in the lacteous appearance of the apocrine sweat.[1]

The growth, development, and activity of these glands have been shown to be related to sexual development and maturation. This facet has been studied extensively from the histologic standpoint, and it can be said that the apocrine gland does not develop until puberty and that after the menopause the apocrine gland shows involutional changes. In women activity of the apocrine gland undergoes cyclic changes (least activity in midmenstrual period; highest activity in premenstrual period; variable activity during pregnancy). No cyclic changes have been shown in men.[2]

In 1922 Schiefferdecker published his monumental treatise on these large sweat glands. It was he who named them apocrine sweat glands. It was his proposal, moreover, that the number of these glands could be the basis for the formulation

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This study was supported by Contract DA-49-007-MD-154 with the Medical Research and Development Board, Office of the Surgeon General, Department of the Army.

1. Woolard, H. H.: The Cutaneous Glands of Man, J. Anat. **64**:415, 1930. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: II. The Apocrine Glands, Arch. Dermat. & Syph. **38**:373 (Sept.) 1938.

2. Cavazzana, P.: Indagini sul comportamento morfo-funzionale delle ghiandole glomerulari apocrine della pelle dell' ascella durante le fasi del ciclo mestruale e nella la gravidanza, Riv. ital. ginec. **30**:114, 1947.

of an anthropological hierarchy. He felt that the fewer apocrine glands present, the greater the racial superiority of the species.[3]

Physiologic studies of this gland have lagged far behind the histologic and the anatomic. Little has been written concerning the control of the apocrine sweat gland, its mode of action, or its physiologic significance.[4] Most of the physiologic observations have been limited to the olfactory perception of apocrine gland activity in times of sexual excitement. Apocryphal accounts of the aphrodisiac properties of apocrine sweat are easy to find. Yet controlled experimental observations are lacking.

To close this gap in our knowledge requires the employment of physiologic methodology in the study of these glands. We have been attempting to apply such techniques to the study of human axillary apocrine gland function,[5] and we should like to review the methods we have followed or are in the process of evaluating.

DIRECT VISUALIZATION OF APOCRINE SWEAT

For direct visualization of apocrine sweat, the axilla is shaved, using either a safety razor or an electric clipper. The patient's arm is extended laterally to keep the axillary vault exposed during the course of observations. Visualization may be achieved with the unaided eye, but preferably observation is through a magnifier, such as an otoscope or a dissecting microscope ($\times$ 15). The apocrine sweat is seen to appear generally at the hair follicle, although in some subjects a relatively large percentage of apocrine glands open independently onto the skin surface, in a manner identical to that of the eccrine sweat glands. The apocrine sweat is a whitish secretion (Fig. 1). This can be seen grossly as the milky drop appears and is in sharp contrast to the colorless eccrine sweat. In doubtful instances the specimen can be collected in a glass micropipette and readily identified by placing the tube on a black background. The secretion of apocrine sweat is small in amount and appears intermittently at any given orifice. If not diluted by eccrine sweat, apocrine sweat dries like glue to form a light-colored plastic solid (Fig. 2). This has a distinctive sheen in all instances and in some may show a type of fluorescence under Wood light. The odor of apocrine sweat varies with different subjects. In some persons the odor is imperceptible; in others the odor gives definite evidence of the presence of apocrine sweat.

The most reliable criteria for the presence of apocrine sweat are (1) appearance at hair follicle orifice, (2) lactescence of fluid, and (3) residue on drying. With the use of this technique, it has been possible to study the effects of emotions (pain, fear, and excitement cause secretion), thermal stress (which has no effect), drugs (the sympathomimetic drugs stimulate, the parasympathomimetic have no effect), and the sympathetic nervous system (which is under investigation).

This direct technique is difficult to employ in the presence of eccrine sweating, which occurs under many stimuli. In routine studies advantage has been taken of the fact that atropine or atropine-like substances completely block cholinergic eccrine

3. Schiefferdecker, P.: Die Hautdrüsen des Menschen und den Säugetiere, ihre Bedeutung sowie die Muscularis sexualis, Zoologica **72**:1, 1922.

4. Olivet, I., and Nauck, E. T.: Histologische Untersuchungen der groben Achselhöhlen-Schweissdrüsen nach Einwirkung von Pilocarpin, Atropin und Adrenalin, Ztschr. ges. exper. Med. **71**:786, 1930.

5. Shelley, W. B.: Apocrine Sweat, J. Invest. Dermat. **17**:255, 1951.

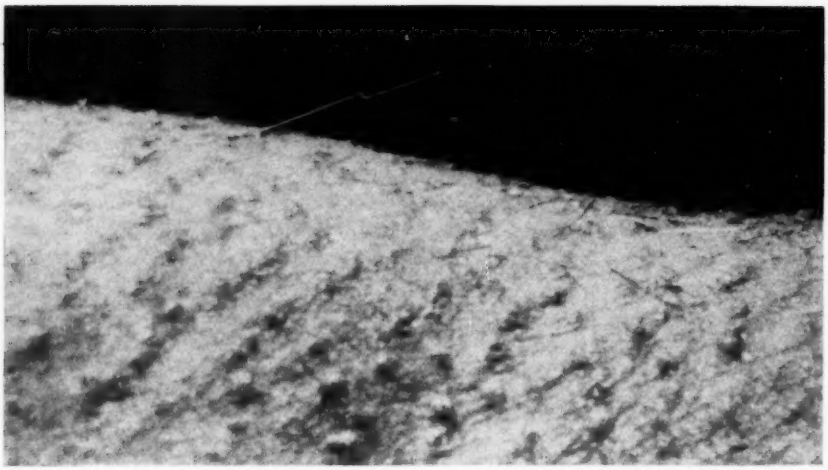

Fig. 1.—Micropipette inserted in pilosebaceous orifice in human axilla. Note whitish apocrine sweat extending halfway up cannula.

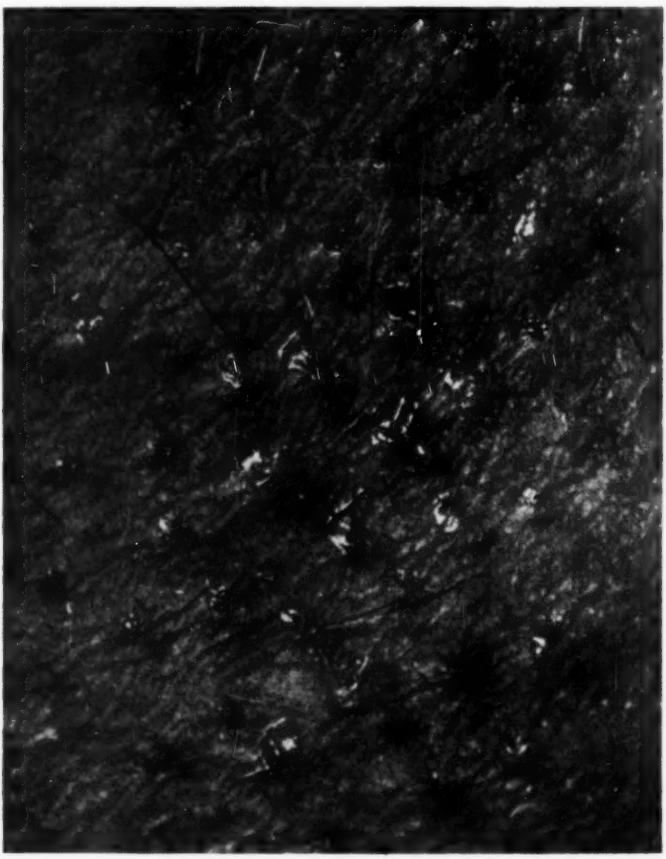

Fig. 2.—Dried apocrine sweat in axilla. Note sheen and umbilication of plaques of solid residue. Apocrine sweating was induced by local injection of epinephrine.

sweating. Since our studies have failed to disclose any action of these atropine compounds on the apocrine gland, they have been used selectively to block eccrine sweating in the axilla. For this purpose an injection of 1 ml. of a sterile 0.1% solution of atropine sulfate is made into the area to be studied. Atropine may also be readily introduced by iontophoresis.

It is possible to enhance the value of direct visualization of apocrine sweat by the insertion of a glass cannula in the duct orifice or the common "apopilosebaceous" orifice (Fig. 1). This intubation technique has also been employed in study of eccrine sweat glands.[6] For this purpose glass capillary tubes of approximately 150-μ bore are inserted a short distance into the hair follicle opening. Such tubes collect microsamples of pure apocrine sweat. In such sweat we have been able to demonstrate the presence of ferric iron, employing the α, α' dipyridyl spot test.[7] The cannulization technique is also being used to study the possibility of "spontaneous" secretion and the role of the myoepithelium. At present we have no physiologic evidence to support the view that the apocrine gland functions continuously in a manner analogous to that of the sebaceous glands. Nor have there been any results to indicate a significant contractile role of the myoepithelium, unless one interprets the secretory response of the gland to epinephrine as an active myoepithelial expulsion of preformed apocrine sweat.

INDIRECT VISUALIZATION OF APOCRINE SWEAT

In many instances it is difficult or even impossible to observe apocrine sweating directly. This is true, for example, in the study of apocrine sweating during various emotional states, psychiatric interviews, or the normal stresses of daily living. The technical limitations of direct visualization in these circumstances necessitate the use of indirect means. Initially it was hoped that some specific constituent of apocrine sweat might be identified on filter paper kept in the axilla during the test period. This has not proved to be satisfactory, in view of the fact that only small amounts of apocrine sweat ever appear. Often the total quantity of apocrine sweat produced is only 0.02 ml. Present spot-test techniques do not permit one to demonstrate consistently the minute quantities of any constituent of apocrine sweat other than water. Thus, we have found that, just as for eccrine sweat, the most sensitive indicators of apocrine sweat are all based on the demonstration of water.

This necessitates the complete inhibition of eccrine sweating. Generally, as noted above, this can be achieved by the local injection of atropine. However, in some persons adrenergic eccrine sweating may be present.[8] To eliminate confusion with this factor, the test papers are reviewed under Wood light, whereby the deposited solids of apocrine sweat can be seen. Eccrine sweat does not contain sufficient solid material to leave any Wood-light-demonstrable residue after evaporation.

Any one of many colorimetric measures used in eccrine sweat studies can be employed for the demonstration of the apocrine sweat. We have used Randall's

6. Takahara, K.: Observations on the Discharge of Sweat from a Single Sweat Gland, J. Orient. Med. **24**:4, 1936.

7. Feigl, F.: Qualitative Analysis by Spot Tests, Inorganic and Organic Applications, Ed. 3, New York, Elsevier Publishing Company, Inc., 1947.

8. Haimovici, H.: Evidence for Adrenergic Sweating in Man, J. Appl. Physiol. **2**:512, 1950.

starch-paper-iodine technique [9] since it is a very simple, yet exact, procedure. The axilla is shaved; atropine sulfate (1 ml. of a 0.1% aqueous solution) is injected into the axillary vault; iodine (1% aqueous solution) is painted over the atropinized area, and a piece of ordinary writing paper or starched filter paper is taped in close contact with the skin, using a backing of cotton batting. Each droplet of sweat produces a purple spot on the test paper. The paper is removed after a suitable interval and is then examined under Wood light for evidence of a deposit of apocrine sweat solids. Semiquantitative observations may be made by counting the number of spots formed in a given area in a given time interval.

Studies are in progress in an attempt to improve the specificity of this demonstration of apocrine sweating. It is hoped that selective staining of the apocrine sweat may be obtained by intradermal injections of a suitable dye.

DIRECT VISUALIZATION OF THE APOCRINE SWEAT GLAND

With the use of enzymatic aids, it is possible in biopsy material to dissect free the apocrine sweat gland and thereby view the entire organ as a unit. The principle involved is the use of hyaluronidase and collagenase [10] to disrupt the fibrous bonds of the surrounding dermis. The details of our technique are being published elsewhere.[11] We have also found certain clearing methods to aid greatly in visualizing the gland.

Similar microdissection procedures have been used previously in investigations on the apocrine gland.[12] It is hoped that our enzymatic method will facilitate observations on the organ hypertrophy and atrophy occurring in various physiologic states.

INDIRECT VISUALIZATION OF THE APOCRINE SWEAT GLAND

It has been known for more than 25 years that a large percentage of persons show numerous iron granules in the apocrine gland secretory segments.[13] This is in sharp contrast to the eccrine gland. We have attempted to use this iron content of the apocrine gland as a means of indirect visualization of the gland in our subjects.

In collaboration with Dr. Philip H. Hodes, of the University of Pennsylvania Medical School Department of Radiology, we have had radiographs made of the axillary region. With the use of soft-tissue techniques, it has not been possible to outline the apocrine glands. However, the use of contrast media is being investigated.

The unique iron metabolism of the apocrine glands also affords one the possibility of employing a radioautographic technique by using radioactive iron, Fe^{59}.

EXPERIMENTAL STIMULATION OF THE APOCRINE SWEAT GLAND

We have employed both pharmacologic and physiologic means to stimulate the apocrine sweat gland. In contrast to the eccrine gland, the apocrine gland does not

9. Randall, W. C.: Sweat Gland Activity and Changing Patterns of Sweat Secretion on the Skin Surface, Am. J. Physiol. **147**:391, 1946.

10. Stoughton, R. B., and Lorincz, A. L.: The Action of Collagenase on Skin and the Anti-Collagenase Factor in Human Serum, J. Invest. Dermat. **16**:43, 1951.

11. Shelley, W. B., and Goloneb, S.: To be published.

12. Groth, W.: Der Verlauf des Drüsenschlauches in den a-Drüsen der Achselhaut des Menschen, Ztschr. mikr.-anat. Forsch. **38**:627, 1935.

13. Homma, H.: On Apocrine Sweat Glands in White and Negro Men and Women, Bull. Johns Hopkins Hosp. **38**:365, 1926.

respond to either acetylcholine or thermal stimulation. Secretion is best produced experimentally by the local injection of epinephrine (0.15 ml. of 0.1% aqueous solution) or by the induction of pain. We have employed a hot wire applicator device for the latter stimulus, but the Hardy pain apparatus may be more satisfactory for this purpose.

The response to these stimuli is currently under study both in normal persons and in patients with dermatoses of the axillary region. The effects of roentgen rays and topical antiperspirants are likewise being investigated.

COMMENT

I have tried to present some of our methods, findings, and goals in the study of the apocrine sweat gland. On the basis of our studies we are in agreement with the view that the human axillary apocrine sweat gland is a vestigial scent gland which is called into action in response to emotions. The clinical applicability of much of this work is still uncertain. However, some of our initial findings in the study of Fox-Fordyce disease indicate that this disorder may be basically a "miliaria apocrina," in other words, an apocrine-sweat-retention miliaria. Acting upon this hypothesis, therapy has been directed toward inhibition of apocrine sweating and the elimination of poral occlusion.

Inhibition of apocrine sweating apparently is not yet within clinical grasp: Roentgen destruction probably requires dosage beyond the safe range; sympathectomy does not appear to abolish apocrine sweating; sympatholytic compounds cannot be given systemically in sufficiently high dosage, and their topical administration is still in the experimental phase. Similar difficulties are met in attempting to eliminate the keratinous plug. This poral occlusion may be on a hormonal basis, but the specific relationship is unknown. Administration of vitamin A in massive doses, orally and intramuscularly, has been without effect in our patients. The need for further knowledge is apparent.

SUMMARY

Methods for the study of the physiology of the human apocrine sweat gland are presented.

Miss Sondra Golomb gave technical assistance. Mr. Robert Morris, of the Deats Photographic Agency, Philadelphia, supplied the photographs.

SOME ASPECTS OF THERAPY OF SWEAT DISTURBANCES

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THE CLINICAL importance of disturbances in sweating is being more and more widely recognized. It has become apparent that the sequelae of such disturbances are responsible for a variety of cutaneous and systemic disorders.[1] The object of this paper is to review briefly some of the available therapeutic measures in relation to the following three categories [2] of sweat disturbances:

I. Hypohidrosis or anhidrosis

II. Hyperhidrosis

III. Dyshidrosis [3] or pathidrosis, i. e., abnormal composition of the sweat, or conditions in which both preceding quantitative disturbances are combined or in which one of the two quantitative disturbances coincides with some other disorder or disorders.

I. THERAPEUTIC MEASURES IN HYPOHIDROSIS OR ANHIDROSIS

Whether the hypohidrosis is functional or due to structural changes in the sweat organ, general measures, such as reduced fluid-intake, rest, and protection from environmental heat and high relative humidity, are likely to prove useful. Unfortunately, from a practical and economic standpoint, most patients find these measures difficult if not impossible to apply.

This paper is the fourth in a Symposium on the Sweat Apparatus presented at the meeting of the Bronx Dermatological Society, Bronx, N. Y., Dec. 20, 1951.

From the Department of Dermatology and Syphilology (Dr. Marion B. Sulzberger, Chairman), The Post-Graduate Medical School of New York University-Bellevue Medical Center, and the Skin and Cancer Unit of New York University Hospital.

1. (*a*) Allen, S. D., and O'Brien, J. O.: Tropical Anidrotic Asthenia, M. J. Australia **2**:335, 1944. (*b*) Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert: Thermogenic Anidrosis, J. A. M. A. **124**:478 (Feb. 19) 1944. (*c*) Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K., Jr.: Tropical Anidrotic Asthenia (Thermogenic Anidrosis) and Its Relationship to Prickly Heat, J. Invest. Dermat. **7**:153, 1946. (*d*) Sulzberger, M. B.; Herrmann, F., and Zak, F. G.: Studies of Sweating: I. Preliminary Report with Particular Emphasis on a Sweat Retention Syndrome, ibid. **9**:221, 1947. (*e*) Miller, O. B.; Herrmann, F., and Rubin, J.: The Effects of Mepacrine Hydrochloride (Atabrine) upon the Human Skin, ibid. **15**:445, 1950.

2. These categories are arbitrary and are used for technical reasons only, since many sweat disturbances cannot be considered within one category alone.

3. This term is deliberately used in a wider sense than has heretofore been customary.

Climate and Climatized Rooms.—The spectacular improvement in many anhidrotic and dyshidrotic conditions and the relief afforded in severe and otherwise intractable forms of the sweat-retention syndrome [1d] after transfer of the patient to geographic areas with a more favorable climate illustrate the importance of environmental climatic conditions in relation to many sweat disturbances. As yet unpublished studies by J. Edward Stern,[4] together with the reports of Eidenoff, of El Paso, Texas,[5] as well as the clinical observations of many dermatologists, leave no doubt that severe, incapacitating forms of atopic dermatitis, of certain lichenoid eruptions, and of numerous other conditions caused or aggravated by sweat retention often subside when the patients are transferred to places with consistently low relative humidity and usually rather high temperatures, such as appropriate parts of Arizona, Texas, and California. For obvious practical reasons, this therapy is applicable to very few patients indeed.

In view of our present concepts of the pathogenetic mechanisms of the sweat-retention syndrome, it is logical to suggest the transfer of the patients to completely air-conditioned or climatized rooms, where controlled atmospheric conditions and deliberate lowering of the relative humidity facilitate evaporation and, thereby, the dissipation of heat from the body. The studies of Sulzberger and Emik on Guam,[6] for example, showed that the incidence of prickly heat could be reduced by nearly 50% when 8 duty hours of every 24 were spent in climatized rooms.

Artificially Induced Sweating and Facilitated Evaporation.—In various conditions in which obstruction of the sweat ducts is either the underlying or a contributory factor, exposure to dry heat and subsequently facilitated evaporation have been found useful. Reports of Marchionini,[7] as well as studies at the New York Skin and Cancer Unit and the Department of Dermatology and Syphilology of The Post-Graduate Medical School of New York University, have confirmed the original findings of Herrmann and Fuerst [8] that some patients suffering from chronic dermatoses, which in recent years were found to be caused or aggravated by sweat retention, respond well to frequent and systematic therapeutic exposures to dry heat.[9]

The procedure is carried out as follows: A reflector-type sweat box with incandescent light bulbs is placed over the trunk of the patient, who must be completely naked. The lights are turned off as soon as sweat droplets are visible. The patient

4. Stern, J. E.: Personal communications to the authors on material to be presented before the 10th International Congress of Dermatology and Syphilology, London, England, July 21-26, 1952.

5. Eidenoff, H.: Effect of Environment on Chronic, Severe and Extensive Itching Dermatoses, J. Invest. Dermat. **14**:241, 1950.

6. Sulzberger, M. B., and Emik, L. O.: Studies on Prickly Heat: I. Clinical and Statistical Findings, J. Invest. Dermat. **7**:53, 1946.

7. Marchionini, A.: Über Schwitzbäderbehandlung bei Hautkrankheiten, Med. Welt **11**: 1306, 1937; Alte und neue Formen der Schwitzbäderbehandlung bei Hautkrankheiten, Zentralbl. Haut- u. Geschlechtskr. **63**:15, 1939; Alte und moderne Formen der Schwitzbäderbehandlung der Hautkrankheiten, Deri hastaliklari ve frengi klinigi arsivi **6**:2136, 1940.

8. Herrmann, F., and Fuerst, K.: Ueber die Schweisssekretion und ihre Bedeutung bei Dermatosen, Dermat. Wchnschr. **88**:397, 1929.

9. I. Rosen, H. Rosenfeld, and F. Krasnow (Arch. Dermat. & Syph. **33**:518 [March] 1936) also obtained favorable and probably comparable results in a variety of conditions, including "neurodermatitis," by exposure to heat; however, the heat cabinet employed by these authors contained air saturated with moisture.

should remain uncovered with limbs in maximal abduction until the sweat has completely evaporated. This procedure has been found to benefit a number of patients suffering from atopic dermatitis aggravated by sweat retention, those with lichenoid eruptions caused by sweat retention, and even some patients having lichen planus. The treatment should be repeated once daily at least, for as many weeks as appear necessary. For the time being, it is assumed that the relief afforded by this procedure may depend to a significant extent on a forcible expulsion of plugs from the sweat ducts by the increased flow of sweat.

In the original studies [10] the concept of the mechanisms possibly responsible for the favorable effect of enforced sweating differed in several points from our present concept. In the early group of patients so treated, sweating was induced by either heat or pilocarpine administration. The group of patients with a favorable response included also subjects with Fox-Fordyce disease and with parapsoriasis.

Vitamin A.—We have long been favorably impressed by the effect of large doses of vitamin A [11] (50,000 units of aqueous vitamin A daily for several months) in some patients with horny plugging of the sweat pores and the signs of sweat retention. The effect perhaps is due to softening of the keratin, leading to decreased formation of horny plugs and loosening of those already present.

Hormones.—When imbalance of endocrine function is suspected of playing a substantial role in the disturbances, endocrine and metabolic studies are indicated, with subsequent administration of suitable hormones, such as thyroid hormones, androgenic steroids, or corticosteroids.

Sodium Salts.—It appears advisable to restrict the intake of sodium salts in serious anhidrosis. Link,[12] Peperhowe,[13] Kuno,[14] Ito and Kosuge,[15] Nishibori,[16] Kashiwabara,[17] and others observed that sweat delivery after exposure to heat or upon physical exertion was significantly retarded and reduced after oral or intravenous administration of sufficient amounts of sodium chloride. That a reduction in the intake of sodium chloride combined with an increased water intake produces a beneficial effect upon miliaria was demonstrated clinically by Horne and Mole [18]

10. Herrmann and Fuerst,[8] Weil, E.: Fox-Fordyce'sche Dermatose, Zentralbl. Haut- u. Geschlechtskr. **28**:515, 1929.

11. In a patient with miliaria rubra, anhidrosis, and inadequate absorption of vitamin A, Lobitz and Kierland (A. M. A. Arch. Dermat. & Syph. **64**:411 [Oct.] 1951) also obtained a favorable response in the initial stages of vitamin A administration.

12. Link, R.: Einnahme von NaCl, ein Mittel zur Verminderung der Schweissbildung bei Phthisikern und auf Märschen und zur Verhütung von Magenstörungen bei Anstrengungen und Hitze, München. med. Wchnschr. **62**:1214, 1915.

13. Peperhowe, H.: Chlornatrium und Chlorkalzium als Antihidrotika, München. med. Wchnschr. **62**:1572, 1915.

14. Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934.

15. Ito, S., and Kosuge, T.: The Effect of Intake of Water and Salt Solution on the Sweat Secretion and on the Regulation of Body Temperature, read before the Thirteenth Congress of the Japanese Physiological Association, 1934.

16. Nishibori, S.: Variation of the Ability to Perspire Due to the Intravenous Injection of Hyper- and Hypotonic Solutions, read before the Thirteenth Congress of the Japanese Physiological Association, 1934.

17. Kashiwabara, K.: Experiments on the Effect of Diaphoretics and Adiaphoretics, J. Orient. Med. **25**:111, 1936.

18. Horne, G. O., and Mole, R. H.: The Effect of Water and Salt Intake on Prickly Heat, Lancet **2**:279, 1949.

and other British investigators,[19] who showed that specifically sodium may be responsible for the production or aggravation of prickly heat. When, instead of such salts as either sodium chloride or sodium dihydrogen phosphate or sodium citrate, ammonium chloride was administered, no comparable deleterious effect was observed.

All these observations with regard to the inhibitory action of the electropositive sodium ion on the outpouring of sweat are in agreement with our hypothesis that an electrophysiologic potential exists along the sweat ducts and has a supporting function in the process of normal sweat delivery. This hypothesis was based in part on observations that externally applied or orally administered electropositive agents tend to inhibit sweat delivery.[20]

Topical Application of Drugs Stimulating the Autonomic Nervous System.—Increased sweating may be induced not only by the systemic but also by the topical application of drugs stimulating the autonomic nervous system. Representative of these are pilocarpine, acetylcholine, and, as shown by both earlier and more recent studies, epinephrine.[21] To induce this effect in situ, these drugs may be injected intracutaneously or applied electrophoretically; the effects, however, are so transitory as to limit the practical value of the methods.

Similarly, external application of 2,4-hexadien-1-ol (hexene-ol®) will noticeably increase thermal sweat delivery in any skin area, but the stimulating action is too brief to be of much promise in therapy.

Topical Application of Hydrophilic Fats.—Increased sweat delivery on the application of wool fat (lanolin) was described by Unna,[22] Wolpert,[23] and Rothman,[24] and more recently confirmed by O'Brien,[25] who obtained a similar effect with several other lipids. Our experimental findings, after the application of wool fat and other hydrophilic ointments and waxes, were substantially the same as those of previous observers. However, these agents were hardly of any clinical use in the treatment of patients with sweat retention.

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19. Fay, F. R., and Susman, E.: On Prickly Heat, M. J. Australia **2**:453, 1945.

20. (*a*) Sulzberger, M. B.; Herrmann, F.; Keller, R., and Pisha, B. V.: Studies of Sweating: III. Experimental Factors Influencing the Function of the Sweat Ducts, J. Invest. Dermat. **14**:91, 1950. (*b*) Miller and others.[1e]

21. Ackerman, A.: Studien zur Physiologie der Schweissdruesen: I. Zur Pharmakologie und Funktionsweise der Schweissdruesen, Dermatologica **79**:151, 1939; II. Bemerkungen zur Innervation der Schweissdruesen, ibid. **79**:305, 1939. Sonnenschein, R.: Local Sweating in Man Induced by Intradermal Epinephrine, Proc. Soc. Exper. Biol. & Med. **71**:654, 1949. Wada, M.: Sudorific Action of Adrenalin on the Human Sweat Glands and Determination of Their Excitability, Science **111**:376, 1950. Haimovici, H.: Evidence for Adrenergic Sweating in Man, Federation Proc. **9**:54, 1950.

22. Unna, P. G.: Kritisches und Historisches über die Lehre von der Schweisssekretion, Schmidts Jahrb. **194**:89, 1882; Ueber die insensible Perspiration der Haut, Verhandl. Kong. inn. Med., 1890, p. 230.

23. Wolpert, H.: Die Wasserdampfabgabe der menschlichen Haut in eingefettetem Zustand, Arch. Hyg. **41**:306, 1901-1902.

24. Rothman, S.: Ueber den Einfluss einiger dermatotherapeutischer Grundsubstanzen auf die insensible Wasserabgabe der Haut, Arch. Dermat. u. Syph. **131**:549, 1921.

25. O'Brien, J. P.: Miliaria Rubra, Tropical Anhidrosis and Anhidrotic Asthenia, Brit. J. Dermat. **59**:125, 1947; The Etiology of Poral Closure: An Experimental Study of Miliaria Rubra, Bullous Impetigo and Related Diseases of the Skin, J. Invest. Dermat. **15**:95, 1950.

Peeling Procedures.—Peeling, induced, for example, by the application of salicylic acid (3 to 10% solution in alcohol) or by exposure to ultraviolet rays, may facilitate sweat delivery. Utmost caution is urged in the use of such procedures, since they may result in an accumulation of horny material at the sweat pores and a consequent aggravation of the sweat-retention syndrome.

II. THERAPEUTIC MEASURES IN HYPERHIDROSIS

It is important at the outset to differentiate between *emotional* and *thermal* hyperhidrosis, since in each case the basic mechanisms are different. Obviously, emotional hyperhidrosis is likely to improve with avoidance of mental and emotional strain, while thermal hyperhidrosis will respond to limitation of physical activity and protection from environmental heat and high relative humidity. Nevertheless, as a general rule, rest is of great benefit in any and all forms of hyperhidrosis. Restriction in the intake of fluids will, understandably, somewhat reduce the quantities of sweat. But a practical application of any of these principles is difficult.

Anticholinergic Drugs.—A. Systemic Application: The systemic use of the "classic" anticholinergic drugs, atropine and scopolamine, or of such drugs as homatropine and adiphenine (trasentine®; 2-diethylaminoethyl diphenylacetate) hydrochloride is severely limited because of their toxic effects and the relatively short periods of relief they afford. It has been established by Shelley and Horvath [26] that a large oral dose of atropine will significantly inhibit sweating (locally induced by topical administration of pilocarpine at different intervals over a given period) for 30 minutes after its administration, but that after another 30 minutes this action is already at an end. These drugs are best administered, therefore, for relatively short periods and on occasions when they may be of decisive value, as, for instance, during attacks of grave sweat-retention syndrome, or prior to anticipated mental stress in emotional hyperhidrosis, or to forestall acute exacerbations in intertriginous areas or on the hands and feet in hyperhidrosis complicated by dyshidrosis.

During the past year, the new anticholinergic compounds methantheline (banthine®) bromide and diphenmethanil ("prantal") methylsulfate have been recommended as suitable for prolonged systemic use, chiefly because of an asserted low incidence of side-effects.

Recently, Brown and Sandler [27] obtained encouraging results with methantheline in the treatment of hyperhidrosis, intertrigo, and eruptions of the hands and feet related to disturbances in sweating. A more or less favorable response to the drug was observed in all 27 of the patients receiving methantheline, while in 74% of the patients the improvement was distinct. Therapeutic amounts of the drug (100 to 200 mg. daily given over an average period of eight weeks) gave rise to initial dryness of the mouth in seven, transient disturbances in ocular accommodation in three, and transitory urinary retention in one of the subjects.

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26. Shelley, W. B., and Horvath, P. N.: Comparative Study on the Effect of Anticholinergic Compounds on Sweating, J. Invest. Dermat. **16**:267, 1951.

27. Brown, C. S., and Sandler, I. L.: Effective Application of Banthine® in Dermatology, A. M. A. Arch. Dermat. & Syph. **64**:431 (Oct.) 1951.

A study of the effects of diphenmethanil on hyperhidrotic conditions of the hands and feet, undertaken by Nelson,[28] yielded favorable results in 8 of 15 patients. Nelson observed a good response to diphenmethanil in one patient in whom methantheline had failed, whereas methantheline helped two patients who had not responded to diphenmethanil. In two patients neither methantheline nor diphenmethanil was found to be of benefit. With the exception of headaches, which occurred in one patient whenever diphenmethanil was administered, no side-effects were observed from this drug.

Our experience with these drugs has so far been too limited to permit an evaluation. Only one of seven patients we treated with methantheline (four to six times 50 mg. daily for periods of one to four weeks) showed some decrease in hyperhidrosis after three weeks, while five complained of dryness of the mouth. Of six hyperhidrotic patients receiving diphenmethanil (four to eight times 50 mg. daily for a period of one to four weeks) two appeared to benefit from the higher doses. Possibly our dosage was too small for the other patients, or the periods of administration of the drugs were too short; we are, therefore, carrying out more extensive trials with different dosage schedules.

Further studies should establish whether or not the new drugs are superior to atropine. In any case, methantheline, in addition to urinary retention and other ill-effects already mentioned, may produce vertigo, salivary oppression, constipation, general weakness, etc.

B. Topical Applications: According to Shelley and Horvath,[26] a single local application of a 1% aqueous solution of scopolamine hydrobromide to hyperhidrotic areas for about 10 minutes can distinctly inhibit sweating for a period of five to eight days. The striking experimental results obtained by these investigators indicate that scopolamine hydrobromide (as well as atropine methyl nitrate and atropine sulfate, which are only slightly less effective) may prove to have some therapeutic significance in the treatment of severe forms of hyperhidrosis. The topical application of scopolamine hydrobromide is definitely contraindicated if dermatitis is present, as toxic amounts of the drug may be absorbed. Unfortunately, the application of these solutions to hyperhidrotic palms and soles appears to be impractical, since absorption is insufficient in these areas.[29]

General Sedatives.—Patients with hyperhidrotic conditions, especially emotional hyperhidrosis, often respond to general sedatives, such as barbiturates in low dosage, bromides (e. g., calcium bromidogalactogluconate [calcibronat®]), or tincture of valerian. As a rule, these sedatives are better tolerated than the anticholinergic alkaloids and are of special value whenever medication over a long period is desirable.

Antihistaminic Drugs.—The report on an "acetylcholine blocking effect" of antihistaminics by Perry, Hosmer, and Sternberg and the discussion of this report

28. Nelson, L. M.: Prantal in the Treatment of Hyperhidrosis, J. Invest. Dermat. **17**:207, 1951.

29. MacKee, G. M.; Sulzberger, M. B.; Herrmann, F., and Baer, R. L.: Histologic Studies on Percutaneous Penetration with Special Reference to the Effect of Vehicles, J. Invest. Dermat. **6**:43, 1945. Herrmann, F.; Sulzberger, M. B., and Baer, R. L.: Penetration of Allergens into the Human Skin, New York J. Med. **44**:2452, 1944. Herrmann, F.: Introduction of Allergens into the Skin by Inunction with "Intraderm": I. Additional Experimental Data on the Inunction Test, Ann. Allergy **3**:431, 1945; II. Desensitization by Allergen Inunctions, ibid. **4**:4, 1946. Shelley and Horvath.[26]

by Cornbleet, Rothman, and Andrews [30] encouraged us to try tripelennamine (pyribenzamine®) and diphenhydramine (benadryl®). Thus far, the results in both emotional and thermal hyperhidrosis have not been promising.

Roentgen Rays.—The application of roentgen rays to hyperhidrotic skin areas is considered useful by most experienced dermatologists, in particular by MacKee,[31] who obtained some of the earliest favorable results with carefully administered doses. Miescher and Boehm [32] recommended divided doses to a total of 1,100 to 1,600 r, with 100 kv., 2 mm. Al filter, and a distance of 30 to 40 cm. This treatment was particularly successful when the hyperhidrosis was continuous rather than intermittent. Needless to say, the application of x-rays to combat hyperhidrosis calls for great skill and caution, since some kind of damage to the sweat organ is apparently responsible for the beneficial effect.

Astringents.—The number of astringent chemicals which are applied externally to counteract excessive sweating, is almost unlimited. As a rule, remedies which are not in some way and to some degree harmful to the skin tissues, either as nonspecific irritants or as potential sensitizers, do not appreciably alleviate hyperhidrosis. This is true, for example, of most common dusting powders, though the late J. Gardner Hopkins and collaborators [33] successfully applied 5% powdered paraformaldehyde mixed with bentonite or talc, without observing any signs of sensitization in 43 patients.

Aqueous solutions of boric acid, resorcinol, potassium permanganate, lead acetate, aluminum subacetate, or tannic acid when applied to hyperhidrotic areas by means of compresses are effective and relatively safe in use. Such treatment, though inconvenient in execution, is of particular value in hyperhidrotic conditions of the hands and feet. It should be mentioned that the more active of these solutions, namely, lead acetate, aluminum subacetate, and notably tannic acid, are potentially irritating to the tissues. Irritation is likely to occur when, as a result of rapid dehydration caused by the astringent, inflammatory exudate or sweat is retained under the altered tissue material.[34] For this reason, solutions of these astringents must, as a rule, be applied for short periods only (about one to two hours daily), and, if continuous application is desired, it should be undertaken under strict supervision.

For applications by patting or dabbing, the choice of a mild or of a strong astringent solution will depend on the severity of the condition and the extent of any irritation already present. Examples of the milder solutions are tannic acid, 1 to 2% in alcohol or glycerin, and potassium permanganate, 1 : 5,000 to 1 : 10,000 in water. Formaldehyde, 5 to 10% solution in water or alcohol, is an example of a more effective, but also more potentially damaging, remedy of this type.

30. Perry, D. J.; Hosmer, J. A., and Sternberg, T. H.: The Acetylcholine "Blocking Effect" of "Antihistaminic" Drugs as Measured by Electrophoresis of Mecholyl in Human Subjects, J. Invest. Dermat. **16**:31, 1951.

31. MacKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in the Treatment of Diseases of the Skin, Ed. 4, Philadelphia, Lea & Febiger, 1946, p. 442.

32. Miescher, G., and Boehm, C.: Roentgen Therapy of Localized Hyperhidrosis: Follow-Up of 192 Treated Patients, Schweiz. med. Wchnschr. **78**:14, 1948.

33. Hopkins, J. G.; Hillegas, A. B.; Ledin, R. B.; Rebell, G. C., and Camp, E.: Treatment of Hyperhidrosis and Symmetric Lividities of Feet, Arch. Dermat. & Syph. **57**:850 (May) 1948.

34. Herrmann, F.: Ueber die Wirkung feuchter Umschlaege, Dermat. Ztschr. **50**:277, 1927.

Electropositive Agents.—In view of the presumptive existence of an electrophysiologic potential along the sweat ducts, with electronegativity at the terminal portion, as demonstrated by a selective affinity of the spiral part for electropositive dyes,[35] clinical trials with "dabbed-on" applications of watery solutions of the quaternary ammonium base benzalkonium (zephiran®) chloride (0.1 to 5%) and lithium iodide (10%) have been inaugurated most recently. Although several patients showed some reduction in hyperhidrosis, it is as yet too early to venture an opinion concerning the possible practical value of these solutions. It is strongly recommended that at the beginning of treatment with benzalkonium chloride high dilutions be used and the patient be carefully observed, as this drug may induce primary irritation, as well as sweat-retention vesicles.[35b]

Application of Galvanic Current and Electrophoresis.—The postulated electrophysiologic potential along the sweat ducts may also be reduced by means of a galvanic current applied to the skin. A possible clinical application of this principle may be inferred from the experiments of Schlachta,[36] Takata,[37] and Shelley, Horvath, Weidman, and Pillsbury,[38] all of whom were able to induce anhidrosis by application of a galvanic current to the skin, preferably with the anode as the active pole. We feel that this procedure may be tried particularly in the treatment of patients with emotional hyperhidrosis, rather than in that of patients with thermal hyperhidrosis, since in our experience the latter are more inclined to inflammatory complications from sweat retention.

Cataphoretic applications of aqueous solutions of formaldehyde to hyperhidrotic skin areas were recommended by Ichihashi.[39] He reported that one series of three to four applications "could stop the suffering entirely at least for 1½ months, sometimes longer than 2 months." Good results were obtained on the palms and soles with a 7.5 to 10% solution of formaldehyde, applied under the anode with a current of 0.33 to 0.5 ma. per square centimeter for 10 minutes; in the axillae, however, a 5 to 7.5% formaldehyde solution and a current of 0.25 to 0.33 ma., applied for five minutes, were necessary for good results. Each course of treatment consisted of a total of three or four applications, given at intervals of about two days.

Ointments.—Of the many ointments employed in hyperhidrotic conditions, the old and proved unguentum diachylon album Hebra (lead oleate ointment) still holds its place, especially in the treatment of exfoliating processes of the palms and soles. Dressings with the ointment are applied overnight or, when feasible, are

35. (*a*) Miller and others.[1e] (*b*) Sulzberger and others.[20a] (*c*) Herrmann, F., and Miller, O. B.: Pharmacologic and Pathogenetic Effects of Mepacrine Chloride (Atabrine) upon the Human Skin, Acta dermat.-venereol. **32**:304, 1952.

36. Schlachta, J.: Ueber experimentelle Erzeugung der Miliaria crystallina, Monatsh. prakt. Dermat. **46**:165, 1908.

37. Takata, K.: Description of Production of Anidrosis by Means of Iontophoresis, Folio Endocrinol. Jap., Vol. 18, Pt. 3, Oct., 1942.

38. Shelley, W. B.; Horvath, P. N.; Weidman, F. D., and Pillsbury, D. M.: Experimental Miliaria in Man: I. Production of Sweat Retention Anhidrosis and Vesicles by Means of Iontophoresis, J. Invest. Dermat. **11**:275, 1948. Shelley, W. B.; Horvath, P. N., and Pillsbury, D. M.: Anhidrosis: An Etiologic Interpretation, Medicine **29**:195, 1950.

39. Ichihashi, T.: Effect of Drugs on the Sweat Glands by Cataphoresis, and an Effective Method for Suppression of Local Sweating: I. Observations on the Effect of Diaphoretics and Adiaphoretics, J. Orient. Med. **25**:101, 1936.

changed only once in every 24 hours. Hopkins and his group [39] recommended polyethylene glycol (carbowax®) with 10 to 20% powdered tannic acid for this purpose.

Antiperspirants in the Axillae.—In discussing the many antiperspirant creams, solutions, and other preparations in use to reduce axillary sweating, we shall confine ourselves to a very brief reference to probable principles of their actions. Experiments with preparations containing aluminum salts have shown [39a] that these salts affect eccrine and apocrine glands differently, damaging the ducts in the former and the glandular epithelium in the latter. Our studies suggest that the epithelium of the apocrine glands is more readily damaged by locally applied antiperspirants than are the ducts of the eccrine glands. This would explain our observation that antiperspirant preparations are much more effective in the axillary vaults than in other skin areas where only eccrine glands are present. Moreover, since a relatively weak influence is capable of sufficiently damaging the apocrine epithelium to reduce sweating without causing ductal or periductal changes, the relatively rare occurrence of papulovesicular and consequent pyodermic eruptions on application of antiperspirant products to the axillae can be more readily understood. In our experience, certain persons are especially inclined to show this eruptive form of sweat retention in response to practically any antiperspirant, and this inclination may be shared by members of the same family.[39a] In any and all persons, unnecessarily frequent application of antiperspirants to the armpits is inadvisable. Persons habitually using an antiperspirant should individually ascertain the longest possible interval between applications which still permits the maintenance of the desired effect. In many instances one or two applications a week are entirely adequate.

III. THERAPEUTIC MEASURES IN DYSHIDROSIS

Maintenance or Repair of Acidification.—Exposure to Dry Heat: Whenever dyshidrotic conditions are complicated by, or associated with, hyperhidrosis or anhidrosis or a combination of the two disorders, the general measures discussed previously may be applied. A large category of dyshidrotic conditions is characterized by a predilection for intertriginous sites, by stagnation of sweat because of inadequate evaporation, by maceration of the skin, and by a defect in the so-called physiologic acid mantle of the skin because of a shift in pH toward alkalinity. In these, the previously described treatment by exposure to dry heat and promotion of free evaporation from the skin surface may be helpful (Part I). With the aid of a few minor technical devices, such as insertion of cork wedges between the distal parts of the toes, we have obtained favorable results with the heating procedure in a number of patients with intertriginous dyshidrosis.

Ventilated Footgear: It is certainly of great practical importance to support as far as possible the natural process of evaporation which maintains dryness and acidification of the skin surface. For this reason, subjects with dyshidrosis of the feet should preferably wear sandals, perforated shoes, or other types of "ventilated" footgear during the summer. Many dermatologists have long advocated this procedure, the efficacy of which was further demonstrated by Nickerson, Irving, and Mehmert in 1945,[40] when they studied the occurrence of athlete's foot (dermato-

39a. Sulzberger, M. B.; Zak, F. G., and Herrmann, F.: Studies of Sweating: II. On the Mechanism of Local Antiperspirants, Arch. Dermat. & Syph. **60**:404, 1949.

40. Nickerson, W. J.; Irving, L., and Mehmert, H. E.: Sandals, and Hygiene and Infections of the Feet, Arch. Dermat. & Syph. **52**:365 (Nov.-Dec.) 1945.

phytosis) in 2,100 men undergoing military training at Eglin Field, Fla., during the summer. Before training, the incidence of clinically significant foot lesions was 23%. The men were divided into two groups. During a training period of two months, the control group wore general-issue boots, while the experimental group wore open-toed sandals. At the end of the training period, the incidence of foot lesions in the control group had risen to 28%, whereas in the experimental group it had dropped to 3.5%, i. e., to one-eighth of the incidence in the other group.

Topical Agents: The simplest of the innumerable topical measures in use in the treatment of dyshidrotic conditions—though often underestimated—still appear to be the most effective. This applies, for example, to bathing in dilute solutions of potassium permanganate, to keeping the involved areas completely dry by careful use of soft towels, and to the regular application of powder.

During the last 12 years, Peck and collaborators,[41] Rothman and his group,[42] and others [43] have clarified the nature of the action of the fatty acids or their salts, which contribute largely to the physiologic resistance of the skin surface to fungous infection. Even before these experiments Marchionini recommended the application of dilute hydrochloric acid, a buffer mixture containing lactic acid, or powdered boric acid to the dyshidrotic area.[44] At present, powders containing undecylenic acid, propionic acid, or caprylate combinations are being used to combat or prevent secondary infection by fungi or bacteria. Sulzberger, Shaw, and Kanof showed that an undecylenic acid-zinc undecylenate powder has significant value in preventing common forms of cutaneous foot trouble in military personnel.[45]

As an essential support of free evaporation from intertriginous dyshidrotic areas, where moisture and alkaline decomposition are apt to aggravate the condition, it is strongly recommended that all affected sites be treated by systematic applications of gauze strips sprinkled with powder. Patients with maceration or a tendency to maceration between the toes, for example, should insert powdered strips of gauze in the interdigital spaces every morning.

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41. Peck, S. M., and Rosenfeld, H.: The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, J. Invest. Dermat. **1**:237, 1938. Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Role of Sweat as a Fungicide, with Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections, Arch. Dermat. & Syph. **39**:126 (Jan.) 1939. Peck, S. M., and Russ, W. R.: Propionate-Caprylate Mixtures in Treatment of Dermatomycoses, with Review of Fatty Acid Therapy in General, ibid. **56**:601 (Nov.) 1947.

42. Shapiro, A. L., and Rothman, S.: Undecylenic Acid in the Treatment of Dermatomycosis, Arch. Dermat. & Syph. **53**:166 (Sept.) 1945. Rothman, S.; Smiljanic, A. M., and Shapiro, A. L.: Fungistatic Action of Hair Fat on Microsporon Audouini, Proc. Soc. Exper. Biol. & Med. **60**:394, 1945.

43. Keeney, E. L.; Ajello, L.; Broyles, E. N., and Lankford, E.: Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and in Vitro: Comparison of Their Fungistatic and Antibacterial Effects with Other Ointments, Bull. Johns Hopkins Hosp. **75**:417, 1944. Keeney, E. L.; Ajello, L.; Lankford, E., and Mary, L.: Sodium Caprylate: A New and Effective Treatment for Dermatomycosis of the Feet, ibid. **77**:422, 1945.

44. Marchionini, A.: Säurebehandlung intertriginoeser Epidermophytien, Dermat. Ztschr. **56**:248, 1929; Zur Pathogenese und Differentialdiagnose dyshidrotischer und dyshidrosiformer Bläschenerkrankungen der Hände und Füsse, Dermat. Ztschr. **58**:222, 1930.

45. Sulzberger, M. B.; Shaw, H. C., and Kanof, A.: Evaluation of Measures Against Common Fungous Infections of Skin, U. S. Navy M. Bull. **45**:237, 1945. Sulzberger, M. B., and Kanof, A.: Undecylenic and Propionic Acids in Prevention and Treatment of Dermatophytosis, Arch. Dermat. & Syph. **55**:391 (March) 1947.

For the same reasons, deformities which interfere with the physiologic process of evaporation, such as flat feet and superimposed toes, should be corrected, whenever feasible.

IV. SUMMARY

A review of some therapeutic measures at present available for the treatment of various sweat disturbances is submitted.

The most consistently effective, but usually least practicable, therapeutic procedure in most sweat disturbances is removal of the patient to a more suitable climate, i. e., one where temperatures are relatively high and relative humidity is low.

Some of the procedures discussed are unquestionably both simple and effective; many of the measures in use or under trial, however, are insufficiently proved or are only partially effective in controlling sweat disturbances, or have too narrow a margin of safety to be accepted as entirely satisfactory.

DISCUSSION

DR. MARION B. SULZBERGER: Of the almost countless features which one might discuss in relation to the presentations by Dr. Hyman, Dr. Lobitz, Dr. Shelley, and Dr. Herrmann, I can select only a very few. The scientific facts that the presenters have placed before us in such magnificent array form a solid foundation upon which I can now venture to build a structure of questions and speculations.

The first feature that I have selected to discuss concerns what happens when the sweat ducts are plugged, plugged hard and fast, so that the sweat which continues to be secreted by the functioning acini of the glands can no longer escape to the surface. O'Brien and his co-workers have termed this situation "internal sweating." It is also the cardinal feature in many forms of what we have called the "sweat-retention syndrome." When one considers that sweat is estimated to have a secretory pressure of 240 mg. of mercury or thereabouts and when one realizes that this pressure is suddenly exerted upon a point smaller than the point of a pin, there is no wonder that this form of sudden application of pressure can lead to a sensation of tickling, pricking, or sharp, sticking pain. There is some evidence that the sensation which is felt when sweat begins to be secreted by a gland that has a firmly plugged ductal orifice is actually due to the distention of the duct (in analogy to that which occurs when other ducts or pipe-like structures are greatly and suddenly distended, for example, the ureters, the urethra, the bile ducts, etc.). Moreover, with firmly occluded ducts and with this tremendous secretory pressure, it is natural that many of the duct walls will lose their normal relative impermeability. The secreted sweat is then not poured out onto the skin's surface but escapes into the tissues, either being forced out through the walls (which may appear to be histopathologically intact) or pouring through actual anatomic, histologically demonstrable ruptures of the walls of the sweat ducts. When one recalls that about 2,000,000 of these sweat glands are estimated to be present in the human skin, it follows that the equivalent of a possible 2,000,000 intracutaneous injections may take place many times daily. That this actually occurs in some cases of tropical anhidrotic asthenia and in certain cases of marked sweat-retention syndrome can be demonstrated both histopathologically and through clinical evidence.

Taking these circumstances as a basis, I should now like to ask five or six related questions.

The first question is the following: Since it is recognized that sweat secretion is regularly stimulated by the emotions, I should like to ask whether it is not conceivable that emotionally conditioned tickling, pricking, and eventually itching may not often be attributable to the effect of the emotions on the sweating and the consequent pressure of sweat which cannot escape through the plugged ducts? In other words, how much of what seems to be a purely psychic mechanism is actually the result of certain psychically induced normal and physiologic responses taking an aberrant course which is attributable solely to the presence of a real structural and anatomic somatic anomaly. How often is psychically produced itching secondary to sweat-pore obstruction and due to the consequent internal sweating and the pressure and distention which results therefrom?

My second question concerns dermatological allergy: How much of allergic sensitization of the skin and elicitation of allergic reactions in the sensitized skin may be due to the repeated intracutaneous injection of sweat which occurs when pores are plugged? And, of course, this sweat may contain in solution or suspension many allergens and potential allergens, i. e., many allergenic substances which are excreted with sweat in ordinary circumstances. These sweat-secreted allergens surely include such drugs as quinacrine, iodides, bromides, and so forth, and possibly also constituents of micro-organisms from foci of infection, as well as allergenic products of foods and of other agents which are ingested, injected, inhaled, or assimilated in some other fashion. To put the question just a little differently: How many times does the fact that a sweat pore is plugged make it possible for sensitizations to take place and allergic dermatoses to be caused to appear through the autogenous, allergenic intracutaneous injection of allergens contained in sweat? And how often is a patient's statement, "I can eat anything while in Arizona [or in New Mexico, etc.], but just let me try the same foods in New York or Chicago and see what happens!" based upon the fact that in one place and climate what little sweat is secreted pours out onto the surface through unobstructed pores, while in the other place and climate the pores are occluded and the sweat, its solutes, and suspended or emulsified constituents are injected repeatedly into the cutaneous tissues.

A third series of questions deals with the problem of how much the obstruction of sweat duct openings contributes to recurrent vesicular eruptions, especially to the troublesome chronic or recurrent recalcitrant dermatoses of the hands, feet, and elsewhere. Is it not possible that in many of these cases the vesicle itself is the result of the sweat retention alone and the vesicle contents consist of the secretion of the sweat gland with a plugged opening? And is it not possible that in other cases not the sweat alone but the allergens in sweat lead then to spongiosis and an allergic eczematous vesiculation? The latter assumption would support, to some measure at least, the possibility that the recurrences and chronicity of some vesicular eruptions of the hands are due to allergens from ingested foods which then appear in the sweat. There is also the possibility that not only vesicular but also lichenoid, papular, and other eruptions are based upon mechanisms analogous to the above but in which the cellular and infiltrative component of the reaction to autochthonous injection of sweat predominates over the vesicular component. You will well realize that these speculations lead to numerous potential explanations, all of which require careful exploration.

A fourth group of queries comes to mind in relation to the above facts of "internal sweating" and "sweat retention." These are the questions which deal with the well-known effects of climates with low humidity, relatively high temperature, low barometric pressure, and adequate but not excessive movement of air upon the cure or amelioration of many forms of itching eruptions and other dermatoses, including atopic dermatitis, other eczematoid eruptions, erythrodermas, and psoriasis. Or to state it somewhat differently, how much of the recognized salubrious effects of climate upon many different kinds of diseases of the skin, of the nasal mucous membranes and of the paranasal sinuses, and of the bronchial tree (as in asthma), and even upon the psyche and the entire individual—how much of these beneficial effects are due to the fact that the maintenance of a proper gradient or differential between the low relative humidity of the air and the humidity of the surface of the organ leads to increased ease of evaporation and of cooling? How much of this ease of evaporation and of cooling leads to rest of the sweat gland apparatus, which is largely relieved of the necessity for constantly repeated, forced secretory activity in order to cool (the function of cooling being largely taken care of by the insensible perspiration when there is the proper gradient of humidity between organ surface and atmosphere)? How much, therefore, of the recovery of these dermatoses is due to the rest and the "splinting" of the sweat glands themselves, when a consistently maintained low environmental humidity allows the glands to recover and their ducts to clear themselves? How much of the improvement is due to the reduction of vesiculation or subsidence of the periductal inflammation due to the lessened need of secretory sweat production and thereby the lessening of the pressures upon the sweat duct and the diminution of extraductal intracutaneous outpourings of sweat and allergens and abatement of the consequent periductal inflammatory responses? How much of the beneficial effects of the maintained proper gradient of humidity between skin surface and environmental air is due to a reduction in the imbibition of the horny material at the skin surface, a consequent reduction in the swelling of the keratin, which then leads to the possibility of a clearing out of the openings of the sweat ducts, a removal of their horny plugs

and of other obstructing material? And as you will all see, this question applies equally to the nose, the sinuses, the bronchial tree, and so forth. In these organs also the proper gradient of the humidity of the air to the humidity of the surface of the organs concerned can lead, just as it does at the skin surface, to a reduction in imbibition and in swelling, which, in turn, can lead to a clearing of the passages and orifices the patency of which is essential for the proper function of the organs concerned.

All these and many more practical as well as fundamental problems of the beneficial effects of climate upon skin diseases will not be properly studied until dermatologists have at their command a sufficient number of specially constructed, completely air-conditioned and climatized rooms. In such controlled rooms one will be able to produce, deliberately and at will, a variety of measured exposures of the patients. They can be exposed, one by one, to different allergens, to different dietary components, to different degrees of relative atmospheric humidity, of heat, of air movement, etc., to different kinds of deliberately produced psychic and emotional stresses; all of these exposures will be in conjunction with the necessary metabolic, endocrinologic, psychologic and psychiatric, and dermatological studies. As soon as such rooms are available, I feel sure that the study of these influences and mechanisms will yield much-needed knowledge concerning many of our common diseases and their management.

But it is not only in relation to the local diseases of the skin and the local diseases of the respiratory tract that it is necessary to engage in studies of the kind which I have just outlined. For the faulty evaporation that leads to faulty cooling leads also to very grave systemic effects—to effects on organs and systems which one would not at first suspect of possibly being related to small, scarcely discernible lesions in the openings of the sweat glands. For example, when a person is unable to cool properly, either through his insensible perspiration or through the pouring out and evaporation of adequate amount of secretory sweat (as occurs, for example, when the sweat glands are blocked in great numbers and when the relative humidity and temperature of the environment are high), under these conditions the person is compelled to adopt vicarious mechanisms in order to attempt to keep his body temperature within the physiologic norms. In these attempts at vicarious cooling, rapid and deep respiration, i. e., panting, is a mechanism often resorted to. This can then lead to the blowing off of too much carbon dioxide and consequently to the manifestations of alkalosis. Another vicarious measure that is sometimes adopted in the attempt to lose heat from a skin which has lost its ability to pour out sweat and to evaporate the necessary amounts of water is vasodilatation of the peripheral vascular tree. This vasodilatation can take on such huge proportions as to lead to an abrupt fall in the diastolic pressure without a corresponding fall in systolic blood pressure. Repeated episodes of the resulting tremendous pulse pressure can then have repercussions upon the entire cardiovascular system and can lead to cardiac changes not essentially different from those which one finds in cases of aortic insufficiency.

These are but a few of the pathogenetic mechanisms that we now recognize can occur as possible consequences of sweat retention. There are, of course, also the well-known discomfort and the varying degrees of hyperthermia which these patients experience when they are forced to undertake any physical exertion in environments of high relative humidity and high temperature. And we are just now beginning to glimpse some of the repercussions of sweat retention, whatever its causes, upon the endocrinologic systems, upon the excretory capacities of the body, upon the adrenocortical influences and their relation to salt and water metabolism. Just as the adrenocortical steroids influence salt and water metabolism, so it is apparent that the capacities of the adrenal cortex, as well as of the entire body, to adjust to stress are in turn influenced by the impaired excretion of salt and water by the kidney and/or the sweat glands.

I hope that this theoretical and speculative addendum to the excellent factual presentations which you have heard previously will perhaps indicate the vast potentialities of further study in these fields. I believe that in this symposium we are getting one of the previews of a new era in cutaneous medicine, an era in which the exact study of the physiologic and pathologic functions of the skin and its appendages is leading to greatly increased knowledge concerning the entire body, its reactions in response to stress and to environment, both in health and in disease. I, for one, have found it fascinating to contemplate the almost unlimited, undreamed-of powerful effects which minute superficial lesions of such small structures as the sweat duct openings can have, not only upon the skin itself, but upon the entire individual, upon his mental state and his physical well-being, upon his capacity to adapt to an environment or his suscepti-

bility to succumb to its effects. That, I think, is the great lesson to be learned here. I am sure that all basic biologic sciences and all medicine will profit from modern dermatological studies of the type which we have been privileged to hear reported.

DR. SANDOR RADO: I feel fortunate in having been invited to discuss before you the psychiatric aspect of sweating, for your symposium shows remarkable advance in knowledge of the physiological changes that underlie the clinical pictures. We psychiatrists, too, are making strides in tracing our clinical findings to the underlying psychodynamics; but then we still face the supreme task of comprehensive medicine: to correlate psychodynamics and physiology.

The physiologist views sweating as one of the homeostatic mechanisms concerned with temperature regulation. However, the sweat mechanism is known also to respond to emotional stimulation. Emotional sweating may aid or disturb temperature regulation; in any case, it may also be charged with functions other than thermal and may have an adaptive value on these other grounds.

In the physiological study of the sweat mechanism one focuses his attention on the interaction of the organism and its physical environment. In the psychiatric study of sweating the focus is on the interaction of the organism and its human environment, for emotions are responses to social situations, arising in the main in the relationship of human beings to one another. The emotions that are known to affect the sweat mechanism are shown in the following paragraphs:

Emergency Emotions.—In this class, emotions are based on (1) the foresight of painful (damaging) experience and (2) the intent to avoid such experience.

Fears: Appropriate or inappropriate fears, fears of conscience, guilt fears. These responses may be manifest or latent. The presence of latent fears can be inferred psychoanalytically from the motivational context.

Rages: Appropriate or inappropriate resentments, angers, and rages. These responses may be manifest or latent. The presence of latent rage can be inferred psychoanalytically from the motivational context. An important automatic discharge of latent yet overflowing rage is self-harming defiance.

Welfare Emotions.—In this class, emotions are based on (1) the foresight of pleasurable (beneficial) experience and (2) the desire for such experience.

Desire: Recognized or unrecognized.

Sexual Excitement: Recognized or unrecognized.

This class further includes emotions (joy, love, pride, etc.) which are not known to affect the sweat mechanism.

Comment.—This classification is based on the adaptive function of the emotions. In my opinion, adaptation is the most helpful point of view we have so far developed in all biology. The psychodynamics of the emergency emotions harmonizes well with Walter B. Cannon's physiological work, which is based on the same point of view.

From among the emergency emotions the varieties of fear just listed have the most conspicuous action on the sweat mechanism. The cold sweat, the clammy palms of the man in fear are generally known. Here we are puzzled by individual differences. We see patients with a healthy capacity for thermal sweating who show no marked emotional sweating when shaking with fear. Other patients may sweat profusely when it requires skillful psychoanalytic exploration to detect their fear. Sweating from fear must be considered a physiological constituent of the organismic event we call fear, even though the adaptive function of this constituent is unknown; however, excessive sweating from fear must be considered pathological: It is a descending involvement.

The adaptive significance of such descending involvement is open to biological speculation. It is a vital interest of the organism to keep its psychodynamic nervous system, its highest level of central integration, free from the burden of excessive excitation. By utilizing the established physiological patterns of the Cannon phenomenon, this system may dump the excessive excitation of faulty emergency emotions at lower physiological levels. The disturbance thus created at the point of dumping is, as a rule, the lesser of two evils. In the light of this hypothesis, descending involvements, such as profuse sweating from fear, originate with a central mechanism for the peripheral disposal of excessive excitation.

Rage frankly expressed appears to have little if any stimulating effect upon the sweat mechanism. But latent rage, if discharged automatically in self-harming defiance, may on the contrary produce profuse emotional sweating. To give a clinical example, there are patients whose manual performance or work requires completely dry fingers; their sweating hands render performance impossible or ruin the material with which they work. The patient thus automatically spites the demanding authority by "cutting off his own nose." After the mechanism of sweating from self-damaging defiance has been established in the organism, it becomes difficult to demonstrate it because of the then added fear of the damaging consequences of the sweating. It then looks as if the sweating would be caused by this fear, which in fact merely intensifies it.

Turning now to the welfare emotions, the sweat-eliciting action of desire appears to have little practical importance. There are reports on performers capable of producing sweating in certain circumscribed areas at will. I myself have never seen this feat. However, I do not think that it can be done by a mere "concentration of thought"; if it can be done at all, one must presume, it is done by the action of desire.

The influence of sexual excitement on apocrine sweating seems to be a controversial question among physiologists. There is nothing controversial about it to the psychiatrist. The huge apocrine sweat glands are strategically located—certainly not for temperature regulation, but for the production of odoriferous sweat. As mentioned by Dr. Shelley, the activity of these glands begins after puberty and is controlled by the hormonal machinery of the organism. There can be little doubt that odoriferous apocrine sweating in the female is a mechanism for the sexual attraction of the male. It may be, as Dr. Shelley has suggested, a vestigial mechanism; however, psychoanalytic observation shows that men in unsuspected numbers and often unbeknown to themselves depend for adequate sexual arousal on this olfactory stimulus. The cultural pattern seeks to make odoriferous sweat sexually repulsive rather than attractive; capitalizing on an idea borrowed from the flowers and the bees, it offers perfume as a vicarious olfactory stimulant.

In reverting to the emergency emotions, let me say a few words about the patient's own emotional reaction to his profuse sweating from fear. This reaction is a composite of shame, embarrassment, and still more fear; the added fear is fear of the damaging social consequences of the profuse sweating. Thus, a vicious circle is brought into play. According to Dr. Herrmann, these patients should be advised to keep cool and calm. Imagine a young man dancing with his "best girl," keeping cool and contemplating calmly the prints his profusely sweating hand will leave on her pink dress. Though Dr. Herrmann's advice is sound, it does not seem to fit every psychological situation. To break these vicious circles is a difficult task even in psychiatric treatment.

Closer correlation of the psychodynamics of the emotions with the physiology of the emotions is still a task for the future.

Dr. David Bloom: I should like to ask Dr. Shelley to comment on the statement that Fox-Fordyce disease is due to a sensitivity to apocrine secretion? Has any work been done to substantiate this?

Dr. Abraham J. Orfuss: Have any newer concepts about colored sweat been advanced?

Dr. George H. Kostant: In studying the apocrine sweat secretion by catheterization of the hair follicles, how do you eliminate any contamination with sebum?

Dr. Emanuel Muskatblit: There are other conceptions of Fox-Fordyce disease. Is it due only to irritation of sweat or to organic hypertrophy of the gland itself?

Dr. Mabel G. Silverberg: Is there any explanation for the fact that aureomycin is so specifically beneficial in infections of the apocrine glands?

Dr. Marion B. Sulzberger: I should like to ask Dr. Shelley whether his inference that the myoepithelium has little or nothing to do with the expulsion of sweat from the apocrine glands is based solely and entirely on his observation that when he catheterizes the duct the sweat does not return from the glass capillary back into the gland, or has he other evidence? It is possible that the capillary pressure and viscosity of the fluid in the little glass tube, as well as the many other forces involved, are such that the sweat is not permitted to be pulled back from the tube by the mere relaxation or the myoepithelial elements.

DR. VICTOR H. WITTEN: Dr. Lobitz mentioned the use of dibenamine® (N, N-dibenyl-beta-chloroethylamine) hydrochloride. It would be helpful to know the availability of this agent and the dosage to be used in a particular site in order to obtain the desired action in clinical applications.

DR. HANS H. BIBERSTEIN: Has Dr. Herrmann had any experience with the use of sage preparation? Years ago the use of this preparation in Europe was found efficacious when taken internally in excessive sweating of palms and soles.

DR. ARTHUR B. HYMAN: There are two schools of opinion on the group into which Fox-Fordyce disease should be placed: one, that the condition is a neurodermatitis, and the other, that the disease is one of the apocrine gland itself. My own experience with the histology is limited. It is my impression that the structure of the glands is not disturbed to a marked degree, and that the picture associated with neurodermatitis is more outstanding.

DR. WALTER C. LOBITZ JR., Hanover, N. H.: Dr. Witten's question regarding dibenamine® hydrochloride is timely. The drug can be obtained through Smith, Kline & French Laboratories, Philadelphia, but I believe it is available only to qualified investigators. Dibenamine® is the most potent adrenergic blocking agent known (Nickerson, M., and Gump, W. S.: *J. Pharmacol. & Exper. Therap.* **97**:25, 1949). It is not active when given by mouth, and the difficulties of intravenous administration plus its potency and duration of action (36 to 96 hours after a single injection) preclude its general use. Dibenamine® has also been used locally by ion transfer into the skin (Sonnenschein, R. R.: *Proc. Soc. Exper. Biol. & Med.* **71**:659, 1949; Last, J. H.; Rodriguez, A., and Pitesky, I.: ibid. **72**:114, 1949).

We have tried to indicate, however, that there are other pharmaceuticals available that are excellent tools for the dermatologist and should be part of his armamentarium in the routine study and diagnosis of the patient's condition in the office and clinic. If, for example, the role of the sweat apparatus is suspected in an eczematous dermatitis (or any dermatosis), the cholinergic sweat can be "turned off" in a local area for days to weeks by the intradermal injection (or ion transfer) of atropine or scopolamine; contrariwise, a similar introduction into the skin of acetylcholine, methacholine (mecholyl®), or carbachol (doryl®) will cause the apparatus to overact and thus make it possible to observe such an effect on the clinical picture. Adrenergic sweating can be "turned on" locally with intradermal (or ion-transfer) application of epinephrine, arterenol, phenylephrine (neo-synephrine®), etc.

The sweat pore can always be easily identified clinically by ion transfer of methylene blue, which will stain this poral opening. Thus, the morphological relationship of the pore to the dermatitis in question is better understood. Of course, locally introduced pilocarpine will act directly on the sweat apparatus and make it function either in producing sweat or in aggravating the sweat-retention clinical picture.

If the clinician is unable to produce local sweating in the area of dermatitis, the biopsy will then tell him whether the sweat apparatus is "plugged" or whether it is totally absent (as is sometimes the case in chronic eczematous dermatoses). However, a biopsy alone without the observations from the standpoint of the clinical physiology and pharmacology can give disappointing information (Holyoke, J. B., and Lobitz, W. C., Jr.: *J. Invest. Dermat.* **18**:147, 1952).

DR. WALTER B. SHELLEY, Philadelphia: I wish to thank those who have engaged in the discussion for their interesting points. I am glad that Dr. Rado mentioned thermal regulation in respect to the apocrine glands. We have found that the apocrine glands do not respond to thermal stress per se. However, we have noted some apocrine sweating in patients exhibiting definite apprehension during our studies on them in the heat cabinet. In regard to the psychodynamics of apocrine sweating, we had hoped that by observations on this type of sweating it would be possible to distinguish various types of emotions. However, this has not proved to be the case, since there is evidence now that it occurs in response to widely different emotions of both the "emergency" and the "welfare" type. Perhaps it is best to view this type of sweating as an adrenergic emotional response.

I know of no studies which would indicate that Fox-Fordyce disease might be the result of a sensitivity to, or an irritation by, apocrine sweat. I feel that the manifestations of Fox-Fordyce disease may well be the result of apocrine sweat retention.

The question of apocrine chromhidrosis is an interesting one. It is possible that some drug or food may react with one of the cellular constituents in the apocrine epithelium to produce an intense color change later to be reflected in the appearance of the sweat. I know of no studies to clarify this, although it is known that stibophen (fuadin®) reacts with ferric iron to produce a blue or red compound, depending upon the pH.

We do not eliminate contamination of the apocrine sweat with sebum completely, since we insert our capillary tube into the hair follicle rather than into the apocrine sweat pore itself. However, from a practical standpoint we consider the amount of sebum contamination negligible. Technical difficulties preclude the ideal intubation of the apocrine sweat pore itself.

I suspect that aureomycin is effective in the treatment of infections of the apocrine gland only in those instances in which the predominant organism is aureomycin-sensitive.

The role of the myoepithelium in apocrine sweat gland function has interested us greatly. Up to the present we have no decisive information on this matter. We have noted that the apocrine sweat in our capillary tubes shows no alteration in level after an initial filling period. Unfortunately, the mechanical limitations of such a system prevent us from drawing any conclusions from this. The problem is under further study with the use of other methods.

DR. FRANZ HERRMANN: In response to questions and comments about my presentation, I reply as follows:

I have had no personal experience with the use of sage preparations, but remember well that they have been recommended.

Mention of the systemic administration of chlorophyll prompts me to admit that I cannot ignore its potentialities as a deodorant.

The findings of Dole and collaborators, mentioned by Dr. Lobitz, that upon cholinergic or thermal stimulation the rate of sweat delivery is paralleled by the sodium concentration in the sweat, apparently support our hypothesis: The electronegative end-portions of the sweat ducts attract the electropositive sodium and water, so that sweat delivery can temporarily be promoted in proportion to the concentration of sodium.

Now I should like to discuss some matters pertaining to Dr. Shelley's presentation.

Dr. Shelley's remarkable study has disclosed a number of basic findings which will open up new avenues for future investigations of the chemical and physiologic significance of the apocrine glands. There are, however, several earlier findings which, at first glance, are difficult to reconcile with some of Dr. Shelley's observations. Thus, the pH of sweat from areas with apocrine glands has generally been regarded as significantly higher than that from areas with only eccrine glands. Pertinent data were presented, for example, by Marchionini (*Arch. Dermat. u. Syph.* **158**:290, 1929), Brill (*Arch. Dermat. u. Syph.* **156**:488, 1928), Herrmann, Behrendt, and Karp (*J. Invest. Dermat.* **7**:215, 1946), and others. In fact, Dr. Shelley's own figure (the pH of freshly secreted apocrine sweat being about 6) seems to confirm this earlier view, since the pH of freshly secreted eccrine sweat ranges at least about 1 unit below that found for the apocrine sweat. The relatively fast rise in pH on the skin surface in the axillary vaults during puberty was explained by the development of the apocrine organs at that age; likewise, the earlier rise in girls than in adolescent boys was interpreted as a consequence of the earlier development of these glands in the former (Marchionini, A.: *Arch. Dermat. u. Syph.* **158**:290, 1929. Herrmann, F.; Behrendt, H., and Karp, F. L.: *J. Invest. Dermat.* **7**:215, 1946). The higher pH values obtained after stimulation of sweating by pilocarpine as compared with the pH of thermal sweat were regarded as due to a relatively stronger response of the apocrine glands to pilocarpine.

This leads me to the question whether Dr. Shelley refers also to the effect of pilocarpine when he states that apocrine glandular activity is not stimulated by either acetylcholine or "the other cholinergic" drugs. It has long been known that pilocarpine induces sweating in horses, which have only apocrine and no eccrine sweat glands (Muto, K.: *Mitt. med. Fakult. Univ. Tokyo* **15**:365, 1916; Langley, J. N., and Bennett, S.: *J. Physiol.* **57**:71, 1923).

Furthermore, several findings suggest that apocrine sweating may be stimulated by heat. Unless one regards our results after exposure to dry heat as some kind of emotional reaction, or as a coincidentally peculiar response of the eccrine glands, our observation of at least a relatively greater amount of thermal sweat in the axillary vaults of females—as compared

with the amount in males (in whom the over-all response was stronger in the areas with eccrine glands)—is understandable in view of the stronger development of the apocrine organs in females (Herrmann, F.; Prose, P. H., and Sulzberger, M. B.: *J. Invest. Dermat.* **18**:71, 1952).

We observed likewise (Prose, P. H.; Baer, R. L., and Herrmann, F.: *J. Invest. Dermat.* **18**:71, 1952) that the quantity of thermogenic sweat in the axillae during puberty exceeds the amount encountered at any other age, a fact which again appears to denote a quantitative influence of the apocrine glands, as the latter are known to develop at puberty. Finally, Z. Felsher (Arch. Dermat & Syph. **49**:410 [June] 1944) of Rothman's group demonstrated sweat secretion by the apocrine glands upon thermal stimulation in a patient with hereditary ectodermal dysplasia in whom eccrine glands were absent but apocrine glands were abundant in the axillae and on the upper chest.

All the data pointing not only toward a higher pH of apocrine sweat, but also toward the possibility of stimulating apocrine glandular activity by heat or by pilocarpine, may be reconciled with the findings presented by Dr. Shelley when the basically dual function of the apocrine glands is taken into consideration. Dr. Shelley himself mentioned this dual function, namely, that these glands produce (1) a viscous and milky material consisting essentially of disintegrated glandular epithelium and (2) liquid sweat by active secretion. It is conceivable that the production of the latter is stimulated by heat or pilocarpine but inhibited by atropine, whereas the former is augmented under the influence of epinephrine, emotional stimulation, pain-sensation, etc., but is not influenced by heat or acetylcholine and is not inhibited by atropine. The liquid phase will probably show the higher pH. Upon atropinization and stimulation by heat, one would expect inhibition of the liquid but not of the milky discharge, in agreement with Dr. Shelley's observation.

The fact that "adrenergic" outpouring of sweat remains unchanged under the influence of atropine, was long ago stressed by Langley and Bennett (*J. Physiol.* **57**:71, 1923). Dr. Sulzberger's opinion that epinephrine may, at least in part, exert its promoting effect on sweat delivery by a direct action on the most peripheral mechanisms of expulsion is supported by some of the earlier data. Thus, Langley and Bennett induced hyperhidrosis in circumscribed skin areas of horses by intradermal injection of epinephrine; these areas subsequently became anhidrotic and remained anhidrotic for some time, while the rest of the skin showed profuse sweating during a period of exercise. This may well be due to transitory evacuation of the lumen of the most peripheral parts of the sweat organ under the influence of epinephrine. Ackerman emphasized that not only the glandular activity but also reabsorption from the sweat ducts and periodic contraction of the myoepithelial elements essentially influence the appearance of sweat; he advanced the concept that small doses of epinephrine facilitate sweat delivery by a decrease of reabsorption from the ducts.

Dr. Walter B. Shelley, Philadelphia: With regard to Dr. Herrmann's comment, we do not feel that pilocarpine will induce apocrine sweating in man. It is true that the apocrine sweat gland in various animals responds to pilocarpine, but we suspect that species differences preclude the possibility of transferring these results to man. Since we have observed that the apocrine glands do not respond to acetylcholine, we would not expect the apocrine gland in man to show an appreciable response to any cholinergic drug or compound. One additional point of significance in interpreting the results in the literature is that local pain of injection may of itself cause apocrine sweating. This might result in misinterpretation of pharmacologic studies.

CAN THE DERMATOLOGIST DO PSYCHOTHERAPY?

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THE PURPOSE of this report is to propose an answer to the question: Can the dermatologist do psychotherapy? We—one a psychiatrist and the other a dermatologist—have worked in more or less close association for several years and have concluded that the answer to this question is a qualified "Yes." In the present report we shall attempt to specify and illustrate the important qualifications which we attach to our affirmative answer: (1) qualifications for the dermatologist; (2) qualifications for the patient; (3) qualifications for the psychotherapy.

QUALIFICATIONS FOR THE DERMATOLOGIST

The dermatologist who asks, "Can I do psychotherapy?" must first ask himself this question: "Do I enjoy helping people to resolve emotional problems, or is it a burden for me to provide this kind of service for patients?" We doubt that a physician could do a good job of psychotherapy if he despised what he was doing. On the other hand, some who find this kind of work very burdensome may find it so largely because of inexperience. Since we tend to enjoy doing what we do well, an inexperienced psychotherapist can hardly expect to find full satisfaction from this work until he has gained some skills and confidence. Nevertheless, some dermatologists will disqualify themselves from doing psychotherapy because they actually find this type of service to patients disagreeable. This is neither surprising nor reprehensible. There are also physicians who find surgical operations, or delivering babies, or treating children disagreeable; and, believe it or not, there are even some physicians who do not particularly enjoy looking at cutaneous lesions. The dermatologist is not obliged to treat emotional disorders himself, but he should be able to recognize such conditions and to recommend referral to a physician who can help the patient with these problems. When a physician has an aversion to the emotional problems of his patients, he must be doubly cautious not to permit his feeling to interfere with the recognition of these disorders when they exist.

In connection with this qualification for the dermatologist, we should also understand that not every physician who enjoys doing psychotherapy is qualified to

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practice it. Occasionally a physician will be motivated to treat the emotional problems of his patients because such treatment provides an opportunity to be authoritative and paternal and to bolster his own ego through manipulating and controlling the lives of others. Unfortunately, the physician who practices psychotherapy for these reasons usually does not recognize such motivations in himself.

Two very practical and important questions concerning qualifications for the dermatologist are these: Does he enjoy listening, and can he sit fairly still for as long as an hour? Some physicians become very restless and uncomfortable if they must sit quietly in a chair for a very long time, as one must during psychotherapeutic interviewing. Others have great difficulty in listening attentively to more than a few minutes of a patient's conversation. Dermatologists who have these difficulties will probably not be able to do psychotherapy successfully. Tense, restless, supercharged physicians must usually leave psychotherapeutic endeavors to more relaxed colleagues.

A further problem concerning the dermatologist as a psychotherapist is the fact that some physicians become anxious and tense when patients tell them personal and intimate details about their lives. This may result partially from inexperience in interviewing patients psychotherapeutically, or it may represent a specific emotional vulnerability on the part of the physician. If after he has gained experience in doing psychotherapy the physician still finds himself anxious and apprehensive during interviews with patients, he may have to forego psychotherapeutic management of emotional disorders. Some of you may be acquainted with a humorous, but at the same time appropriate, aphorism in psychiatry: that "Psychotherapy is a relationship between two people, one of whom is anxious, preferably not the therapist."

Another qualification for the dermatologist is this: If he proposes to do psychotherapy, his own life situation should be sufficiently rewarding and gratifying that he is not consistently preoccupied with worries, anxieties, and conflicts of his own. If he were so preoccupied, he might use his psychotherapeutic relationships with patients to provide the personal satisfactions which should arise from nonprofessional sources. To practice psychotherapy successfully, the physician should be relatively free from serious psychological problems himself. If he is aware of such problems in himself, or if others have called his attention to problems which consistently interfere in his relationships with people, the physician would do well to have these conditions corrected psychotherapeutically before attempting to practice psychotherapy himself. Psychiatrists frequently include as part of their training a personal psychotherapeutic or psychoanalytic experience. As more and more physicians who are not psychiatrists begin to practice psychotherapy, and as these physicians extend the types of psychotherapy which they do, they will find that the psychotherapist must understand himself before he can successfully understand and help his patient.

The dermatologist's level of training in dynamic psychiatry and psychotherapy also influences the decision regarding his qualifications for practicing psychotherapy. Those who have had little or no training along these lines usually should not attempt to use psychotherapeutic methods without supervision. Such physicians, however, can often utilize psychotherapeutic principles, such as a humanistic approach to the patient, recognition of the role of emotional factors in disease, and skillful preparation of the emotionally disturbed patient for psychiatric referral. Those dermatologists

who have had good basic training in dynamic psychiatry and psychotherapy can often do certain types of psychotherapy successfully and with supervision may be able to learn somewhat more technical and difficult methods. Actually, very few dermatologists have had good basic training in dynamic psychiatry and psychotherapy, and many assume that such training is impossible to obtain. It is certainly not easy to obtain training in this field, but some such training opportunities are becoming available. Occasional postgraduate courses in this subject are offered to physicians without psychiatric training, and psychosomatic forums are springing up, principally at medical centers, throughout the country. Two years ago such a forum was started in Indianapolis, the orginal group consisting of a few psychiatrists and several physicians who had no psychiatric training from fields such as internal medicine, dermatology, ophthalmology, allergy, and pediatrics. Another source of such training is private supervision by a psychiatrist, in which the physician consults the psychiatrist at regular intervals concerning patients he is attempting to help psychotherapeutically. In addition, certain textbooks have been published recently which are designed specifically for the needs of the physician without psychiatric training.[1]

One final qualification for the dermatologist has to do with an economic problem. Psychotherapy takes more time than do many forms of medical treatment, and as a result the physician who practices psychotherapy is unable to see as many patients as he would otherwise. This factor may tend to bring about a lowering of his income, to which he sometimes reacts with disappointment and resentment in relation to his use of psychotherapy. Some dermatologists are prepared to accept a somewhat lower income, because in their cases it would not materially affect the living standard for themselves or their families. Other dermatologists, however, whose incomes are already marginal, might jeopardize their living standards by devoting very much time to psychotherapy. In such an instance it is doubtful whether the dermatologist could practice psychotherapy happily and without anxiety regarding its effect upon his economic status. This difficulty can sometimes be overcome by raising the fee appropriately when additional time is devoted to psychotherapy.

Following are three brief illustrations of how these qualifications for the dermatologist apply to the question of whether he can do psychotherapy.

Case 1.—A dermatological resident wished to learn some psychotherapeutic techniques; so one of us (P.F.D.S.) agreed to instruct him. He was a conscientious and sincere physician who seemed well motivated to learn psychotherapy. However, he was an extremely kinetic, talkative, and energetic person who was known among his colleagues for his characteristic dashing about the clinic and general push of activity. In conversations he was very spontaneous and interesting but did much more talking than listening. In social gatherings he was typically the "life of the party." He was assigned a patient with circumscribed neurodermatitis whom he was to interview psychotherapeutically for one hour once a week. The instructor went over the resident's notes with him after each psychotherapeutic session. He lasted for only three interviews. During the first interview he was fairly comfortable because the time was spent in obtaining a past personal history, which gave him an opportunity to ask questions. He became restless and bored during the second interview, when the patient did most of the talking, and he found that the only way he could tolerate sitting quietly for so long was to engage the patient in conversation. In the third interview he tried very hard to sit back and listen, but as the

1. Levine, M.: Psychotherapy in Medical Practice, New York, The Macmillan Company, 1945. Teaching Psychotherapeutic Medicine, edited by H. L. Witmer, New York, Commonwealth Fund, Division of Publications, 1947.

hour went on he became more and more agitated for want of some kind of physical activity. He found himself drumming his fingers on the desk, which caused the patient to block. At the end of the interview he told the instructor that he would have to postpone his ambitions to be a psychotherapist until he could learn to relax.

This case illustrates how some physicians, despite a deep and sincere wish to help patients with their emotional problems, may be unable to do so because of constitutional and characterological factors which make psychotherapeutic interviewing intolerable for them.

CASE 2.—A dermatological resident expressed unusual understanding of the emotional problems confronting a middle-aged, lonely man with generalized neurodermatitis. He was encouraged by one of us (P.F.D.S.) to try to help the patient by means of supervised psychotherapeutic interviews. The resident was very young and inexperienced but was a moderately relaxed and reflective person. During initial interviews with the patient he became uneasy about the responsibility he was assuming in relation to the homeless, friendless man, and some anxiety developed regarding the patient's growing fondness of him. Discussing the case with the instructor reassured him (partly through sharing of the responsibility), and he continued to see the patient for weekly psychotherapeutic interviews over a period of several months. He was a good listener and would sit back in his chair, meditatively puffing on his pipe as the patient did the talking. The patient made a rapid recovery from his cutaneous disorder and moved back into the stream of life.

This case illustrates how even a very young and relatively inexperienced physician was able to employ psychotherapy successfully, despite some initial anxiety about the procedure. He enjoyed doing it; he was able to sit back and listen, and he was not handicapped by serious psychological problems in himself.

CASE 3.—Without the knowledge of one of us (P.F.D.S.), a dermatological resident attempted to treat a patient with pruritus ani psychotherapeutically. The resident was a clever, ambitious person with a great deal of initiative and self-confidence. He had heard the instructor describe an experimental brief psychotherapeutic method which he was investigating in patients with psychocutaneous excoriation syndromes; so the resident decided to try it himself. Without prior training in dynamic psychiatry or psychotherapy, and without supervision of his work with this patient, he began interviewing the patient weekly, focusing his efforts upon the uncovering of repressed rage. During the fifth interview with the patient the resident phoned the instructor; he sounded very upset and frightened and asked whether the instructor would please see the patient for him immediately. The instructor went to one of the clinic rooms, where the patient was found in the process of a violent abreaction of rage, while the very frightened resident tried in vain to calm him down. The instructor had to take over the case then and there, because the resident was clearly too terrified at the monster he had created to continue with the treatment.

This case illustrates that physicians with inadequate training in dynamic psychiatry and psychotherapy should not attempt to use advanced psychotherapeutic techniques and that supervised experience is usually necessary in learning psychotherapy.

QUALIFICIATIONS FOR THE PATIENT

In general, the patients whom the dermatologists can often help psychotherapeutically are those whose illnesses are not too long-standing and those who have a past history of relatively good adjustment socially, maritally, sexually, and occupationally. The patient who might be termed ideal for the dermatologist to manage psychotherapeutically is one in whom the emotional disturbance is primarily current and situational—i. e., a patient whose past adjustment has been good, and in whom a psychocutaneous disorder has developed under the stress of recent conflicts brought

about by his present life situations. Such patients can often be helped by psychotherapeutic methods which are within the grasp of the dermatologist.

On the other hand, patients with long-standing illnesses and past histories of relatively poor adjustment throughout their lives are usually not good candidates for psychotherapeutic management by the dermatologist. Their conflicts are not recent in orgin but usually extend far back into early years of their lives. Current pressures may have aggravated the present condition, but fundamentally the emotional disorder is too deeply rooted in the character and personality of the patient to be managed successfully by a nonpsychiatrically trained physician.

The following two experiences from the practice of one of us (J.S.G.) will illustrate the importance of these qualifications for the patient.

Case 4.—The patient was a 52-year-old woman who had complained of pruritus ani et vulvae of 20 years' duration. There had been an occasional period of complete remission, the longest lasting six months. She had seen many physicians in the past several years because of multiple complaints and had received x-rays to tolerance, vitamin injections, histamine desensitization, estrogen parenterally, liver, barbiturates, codeine, and meperidine (demerol®) hydrochloride to the point of addiction. She had seen a physician weekly for many years because of migraine, "dry heaves," menopausal syndrome, cardiac arrhythmias, and backaches.

She had never married. She operated a small rooming house and earned a living by doing laundry in her apartment. She was one of three children, and her parents were still living. Since her parents were elderly and not well and since she was the only single child, she was constantly being harassed by the family to return home and care for the parents. She was aware of considerable feeling of guilt in connection with this family situation, and her condition became worse with each visit to the home of her parents. She denied any love affairs, but she had developed a strong love for a child who was placed in her care at an early age and felt a great deal of resentment when this child was finally taken back by her own mother.

The patient never went to the movies, feeling that they were evil, and she had no friends to visit except her family. Except for going to the physician's office, the drugstore, and the grocery, she never ventured out. She was easily upset by the failure of a washing machine or an iron, and distressing symptoms would invariably develop whenever minor irritations of this kind arose.

She was seen for a total of 10 psychotherapeutic interviews, during which time no progress was noted except some improvement of the eczematous process about the perineum.

This case illustrates that patients with long-standing illnesses and with past histories of relatively poor social, occupational, sexual, and marital adjustment are not usually good candidates for psychotherapy by the dermatologist.

Case 5.—A 33-year-old married woman consulted one of us (J.S.G.) because of a dermatitis of the antecubital spaces, which had been present for five months. She had never had any cutaneous eruptions prior to the present illness. Examination revealed an eczematous, scaling, moderately lichenified eruption of both antecubital spaces. Itching was worse at night, and she often awakened scratching. Previous treatment had consisted of elimination diets, use of compresses, superficial x-ray therapy, administration of vitamin B_{12}, and various local applications. Scratch and patch tests had been done but revealed no positive reactions. Except for the cutaneous symptoms, the system review was noncontributory. The past personal history revealed that her social, educational, sexual, and marital adjustment had been relatively good. Evidence was obtained in the personal history which suggested that a current situational conflict may have been responsible for initiating, aggravating, and perpetuating her cutaneous disorder. This conflict was concerned with the fact that her mother, who had always dominated her, had come to live at her home. The patient, who was happily married and had two children of her own, silently resented the mother's intrusion in her family and was unable to express her feelings of anger when the mother interfered in the management of the children and the home. In fact, she felt very guilty and ashamed about her resentment toward her mother, considering these feelings to be disloyal and disrespectful. Since the duration of the present illness was not

very long, and because the past personal history revealed evidence of relatively good emotional adjustment, the dermatologist decided to attempt to help the patient with her current situational problems by means of psychotherapeutic interviewing. First, he explained in common-sense terms how emotional tension is frequently responsible for physical illness. Then he asked the patient whether she would be interested in talking to him about whatever problems she had confronting her, so that possibly together they could work out some means of reducing the tensions which were contributing to her illness. She seemed pleased by the physician's display of interest in her and her problems and said that she had wondered from the outset of her illness whether the condition might be related to emotional upsets. She had asked the previous physicians about this possibility, but they had consistently minimized the importance of emotional factors, insisting that her cutaneous disorder was caused by allergenic foods, or contactants, or vitamin deficiency, or infectious agents. Three psychotherapeutic interviews were devoted to discussing her feelings about current problems, principally her conflict about the mother's presence in the household. By the time she returned for her next interview, she had spontaneously discussed the matter with her mother, and they had agreed it would be best for the mother to return to her own home. They remained on cordial terms, and the patient was very relieved that it had been possible to work out the solution so amicably. She expressed gratitude to the dermatologist for taking the time to help her come to terms with the problem, and said that she doubted that she would ever have been able to face it realistically without such help. The cutaneous disorder disappeared promptly and did not recur.

This case illustrates an almost "ideal" type of problem for the dermatologist to manage psychotherapeutically: The illness was not too long-standing, the past history was characterized by relatively good emotional adjustment, and current situational conflicts were largely responsible for the patient's present illness.

The next qualification for the patient arises from the fact that certain diagnostic categories of psychological illness are notoriously difficult to manage psychotherapeutically. These disorders include the psychoses, severe neuroses, and psychopathic disorders. The dermatologist should learn to recognize these illnesses diagnostically and should not attempt to treat them psychotherapeutically. In addition, it is doubtful whether the dermatologist should attempt to do psychotherapy with children, although he may often be able to help children who have psychocutaneous problems by psychotherapeutic work with the parents. Patients with psychotic, severe neurotic, and psychopathic disorders, and children requiring psychotherapy, should be referred to psychiatrists. The following case illustrates the difficulty one of us (J. S. G.) met in attempting to do psychotherapy with a patient having a severe neurosis.

CASE 6.—The patient was a 44-year-old divorced woman who had complained of itching of the eyelids, a condition which had been present for approximately six weeks. An examination revealed a mild eczematous reaction of the eyelids and dug-out excoriations of the neck and cheeks. Previous therapy had consisted of local applications of alcohol and ointments and two x-ray treatments. At first the patient was treated by dermatological and general medical measures: avoidance of all cosmetics, hair shampoos, rinses, local medications, clothing dyes, repellents, certain articles of wearing apparel, and cleaning fluids; in addition, elimination diets and local treatment were prescribed. When these therapeutic measures failed to bring about improvement and as the dermatologist's further contact with the patient began to reveal considerable evidence of emotional tension, he decided to obtain more information about her personal history. Although the patient was not very communicative about her past personal history, the physician learned that she had lost both of her parents at the age of 6 years and had had a fairly stormy life emotionally ever since that time. She had never had good social relationships, had been married once, to an alcoholic, and divorced, had never had a successful relationship with a man, and was occupationally unstable. For many years she had had periodic episodes of depression, in which she was subject to prolonged weeping and marked, uncontrolled jerking

of her body. She required hospitalization at one time for such an attack. Despite the fact that this information strongly suggested the presence of a severe neurotic personality disturbance, the dermatologist attempted to help the patient by means of psychotherapeutic interviewing. It quickly became apparent that this was a mistake, because the patient became increasingly depressed and began to have severe jerking spells. The physician then realized that the patient's psychological illness was far too serious for him to manage; so he referred the patient to a psychiatrist. The psychiatrist corroborated his impression that she was seriously ill psychiatrically and hospitalized the patient for prolonged and intensive treatment.

This case illustrates that patients with psychoses, severe neuroses, and psychopathic disorders should not be treated psychotherapeutically by the dermatologist, but should be referred to a psychiatrist.

Many of the patients who consult the dermatologist are somewhat too difficult for him to manage psychotherapeutically, but they refuse referral to a psychiatrist. In these cases the dermatologist must confine his psychotherapeutic efforts to humanistic, supportive, reassuring methods and must avoid permitting the patient to probe deeply into old memories and conflicts. The mere showing of kindly interest and giving the patient a few added minutes to talk about himself and his suffering will often go far toward shifting the emotional balance in the direction of happiness and health. The following case illustrates the successful use of an emotionally supportive physician-patient relationship. The patient's psychological problems were actually too difficult for a dermatologist to manage psychotherapeutically, but the patient refused psychiatric referral.

Case 7.—A 39-year-old man consulted one of us (J.S.G.) because of an excoriated, scaling, lichenified eruption of the forearms, neck, and face which had been present since the age of 18 years. Numerous physicians had treated him without success. Since every other therapeutic approach had failed, and because this dermatologist detected considerable evidence of emotional tension, a past personal history was obtained. The personal history revealed that his illness had begun shortly after his father's death, and that he had never actually recovered psychologically from the loss of his parents. He had worked very hard, literally driving himself to excel in his occupation as a salesman, and had shown considerable capacity for assuming responsibility in his work and his marriage. His social adjustment was also found to be relatively good, although here, too, he tended to be overly ambitious and driving. This dermatologist recognized that the psychological problems confronting the patient were not contemporary but remote in origin, and that he should be treated psychotherapeutically by a psychiatrist. The patient, however, categorically refused to consult a psychiatrist, although he accepted the importance of emotional factors in aggravating and perpetuating his cutaneous disease. While continuing to treat the patient dermatologically, therefore, the physician attempted to help him by means of a sympathetic, encouraging psychotherapeutic approach which involved talks with the patient each time he came to the office. For a time it seemed that the patient would become inseparably dependent upon the dermatologist, and at one point during the treatment period mild asthmatic attacks developed when the patient felt anxious about the possibility of the physician's terminating treatment. Gradually the patient developed more and more confidence and independence and was able to get along satisfactorily with one appointment a month. His cutaneous disorder disappeared coincident with his ability to carry on independently of the physician. He still occasionally comes in to see the dermatologist for talks when he feels discouraged, but otherwise is making a relatively good life adjustment without further psychosomatic illness.

This case illustrates that some patients whose psychological problems are too difficult for the dermatologist to manage psychotherapeutically may, nevertheless, refuse referral to a psychiatrist. When this happens, the dermatologist may sometimes be able to help the patient to a certain extent through psychotherapeutic aspects of the physician-patient relationship. In the present case the dermatologist became

a parental supporting figure for a patient who had never quite recovered from the loss of his parents. The patient's dependency upon the physician skirted dangerously close to neurotic invalidism in this particular case, but, fortunately, the physician kept his head and managed to help the patient regain his confidence and independence through patient encouragement and support.

The final qualification that we shall suggest in connection with the patient is this: There are some types of psychocutaneous disorders which the dermatologist may often manage psychotherapeutically with safety and success; there are other types of psychosomatic skin diseases which he should usually not attempt to treat in this way. The psychocutaneous disorders in which the dermatologist may often successfully employ psychotherapeutic methods include circumscribed neurodermatitis, eczematous hand eruptions, neuroseborrheic eruptions, urticaria, rosacea, lichen planus, and alopecia areata. The following types of psychocutaneous disorders are usually too difficult for the dermatologist to treat psychotherapeutically: delusions of parasitosis, acarophobia, long-standing atopic dermatitis, anal and genital pruritus syndromes, and dermatitis herpetiformis. In the last analysis, however, the choice of cases for psychotherapeutic management by the dermatologist should depend primarily upon the nature of the patient and his personality rather than upon the type of skin disease. The following two cases illustrate the importance of selecting patients for psychotherapy primarily on the basis of the extent of psychopathology and secondarily in terms of the variety of psychocutaneous disorder.

Case 8.—Several years ago a young man with dermatitis herpetiformis was referred to one of us (P.F.D.S.) for psychiatric evaluation. At that time this psychiatrist had had no previous experience with patients having dermatitis herpetiformis, and he could find no reports in the literature which provided information concerning psychopathology in patients with Duhring's disease. Four interview hours were devoted to obtaining a detailed psychiatric history, which revealed that the young man's emotional adjustment had been very poor since infancy. After the fourth evaluation interview there developed a sudden, acute psychotic break (schizophrenic reaction), which might have been forestalled if this psychiatrist had not explored the past personal history in such detail.

In retrospect, sufficient indication of the impending psychosis was available in the first interview, and if this psychiatrist had noted the evidence of serious psychological disturbance at that time, he certainly would not have proceeded as he did. Since that time, one of us (P. F. D. S.) has had the opportunity to carry out psychiatric studies on six patients with dermatitis herpetiformis, all of whom revealed very serious personality disturbances. Three of the six patients were schizophrenic, and the other three were schizoid personalities. Consequently, we list dermatitis herpetiformis among the skin diseases which the dermatologist should not attempt to treat psychotherapeutically.

Case 9.—One of us (J.S.G.) was consulted by a 45-year-old pharmacist in whom a plaque of circumscribed neurodermatitis had developed on the mesial aspect of the right ankle four years previously. The past personal history revealed evidence of relatively good social, sexual, and occupational adjustment, but evidence was obtained which indicated that the onset of his cutaneous disorder had been associated with a period of marked family tension. He had married a woman of different religious faith from his own and had been ostracized by his family as a consequence of this. His wife subsequently became psychotic, and, during a considerable part of her illness, he nursed her himself. He had lost his business during this period of difficulty, and his family had made life more miserable by jubilantly exclaiming that all these developments proved how foolish he had been to marry outside the family faith. In spite of the many problems he had to contend with, he continued to carry on in a very responsible and

courageous manner. This dermatologist decided to employ psychotherapeutic management in view of the not too long-standing nature of the patient's illness, the evidence of good potential for mature adjustment, and the primarily current and situational aspects of his psychological conflicts. In addition, the type of psychocutaneous disorder involved in this case was one which can frequently be managed psychotherapeutically by physicians without psychiatric training. Seven interviews were devoted to discussion of the patient's current situational conflicts and his feelings in connection with these problems. In the process of discussing these matters, he gradually became able to express considerable feeling of resentment toward his family for their unkind behavior toward him, and also overcame some of the shame and guilt he felt in connection with mixed reactions to his wife's illness. By the fifth interview his cutaneous disorder was on the wane, following an initial period in which it had been aggravated to some extent by the therapy. At the end of the seven interviews the patient's skin was clear and has remained so during the following year. He stopped in to see the physician several months later to express his gratitude again, and to convey the good news that his wife had recovered from her illness and that his family had finally accepted their marriage.

This case illustrates that by selecting patients for psychotherapy primarily on the basis of extent of psychopathology, and secondarily on the basis of type of psychocutaneous disorder, the dermatologist may minimize the errors he might otherwise make in deciding which patients he may safely and successfully treat in this way.

QUALIFICATIONS FOR THE PSYCHOTHERAPY

In general, unless the dermatologist has had unusual training in dynamic psychiatry and psychotherapy, he should confine his psychotherapeutic activities to supportive methods which do not involve extensive exploration of the deeper layers of the personality. Penetrating, excavating, extensively uncovering, and cathartic methods of psychotherapy are procedures strictly for psychiatric specialists and should not be attempted by physicians who lack special training in the use of these highly technical therapeutic methods. Mildly cathartic or ventilative methods may sometimes be employed to advantage by the dermatologist, provided he has had supervised training in the use of these techniques and provided he encourages the liberation of previously unexpressed impulses, feeling, and thoughts only in connection with contemporary conflicts. In almost no conceivable circumstance would it be appropriate for the dermatologist to uncover old, deeply repressed conflicts associated with infancy, childhood, or the remote past.

For the most part, the dermatologist should not include among his primary psychotherapeutic aims the excavation of unconscious material. A limited amount of uncovering is permissible in relation to current problems, but the dermatologist's major psychotherapeutic efforts should be toward strengthening rather than eliminating the forces of repression. This means that by reassurance and sympathetic support the nonpsychiatrically trained physician consistently reinforces the patient's defenses against repressed impulses and feelings, repeatedly emphasizes his capacity for adjustment, and patiently reiterates that there are forces within the patient's personality which are constantly striving toward harmony and health. This is supportive psychotherapy which can often be employed very successfully by physicians without psychiatric training. This is the kind of psychotherapy which helps the patient to regain a feeling of organization in his life, and a feeling of personal confidence and which relegates disturbing impulses, feelings, and thoughts to the background of the psychological life. Much of the success of this type of psychotherapeutic approach depends upon the degree of rapport in the physician-

patient relationship. If the patient feels a high level of confidence in the physician, the physician's quiet, steady reassurance will tend to bring about a feeling of certainty and harmony in the patient. The physician's repeated expression of confidence in the patient helps the patient to believe in himself. Similarly, the physician's praise for the mature aspects of the patient's personality tends to reinforce or strengthen these elements of behavior, and, partly because the physician approves of these elements, the patient begins to exploit his potential for mature adjustment and to become less preoccupied with disturbing and unsatisfying aspects of his life.

Just as the dermatologist should not usually attempt to uncover unconscious conflicts, he should also not strive primarily for the development of insight. Bombarding the patient with interpretations and explanations is psychotherapeutically naive, as well as futile.

The following two case reports are examples of an overly ambitious psychotherapeutic effort by a dermatologist and a more modest but successful attempt in another instance.

Case 10.—A 29-year-old married woman with a pruritic, excoriated, lichenified eruption of both antecubital spaces consulted one of us (J.S.G.). She had had the eruption for nine years, and almost every conceivable type of medical and dermatological treatment had failed to bring about improvement. The past personal history revealed considerable unresolved feeling about the death of her mother and her father's remarriage while the patient was in her late teens. Within a short time after these difficult experiences, she married, and after the birth of the first child the cutaneous disorder developed. This dermatologist recognized that the illness was somewhat too long-standing for him to attempt psychotherapeutic management and that the patient's psychological conflicts were more remote than recent in origin. Nevertheless, he attempted to help the patient by means of psychotherapeutic interviewing, in which he cautiously began to uncover some of her hitherto unconscious feelings about her mother's death, the father's remarriage, her own marriage, and her feelings toward her children. This was a mistake. Although well intended, it was too much for the patient, who began to have marked feelings of anxiety, nausea, vomiting, "nervous chills," and feelings of confusion and dread. The physician recognized this evidence of impending breakdown of repression, and so he sedated the patient and discontinued the psychotherapeutic interviews. Fortunately, the patient retained her contact with reality and was not overwhelmed by the mounting anxiety which treatment had precipitated.

This case illustrates that deeply penetrating and uncovering types of psychotherapy can sometimes liberate previously unexpressed (unconscious) impulses, feelings, and thoughts more rapidly than the patient can integrate them into awareness. When this happens, the patient experiences marked anxiety, which may tend to increase to a point that is intolerable and is reacted to with profound neurotic or even psychotic regressive defenses. The dermatologist should not attempt to use these exploratory, cathartic, deeply penetrating psychotherapeutic methods. Psychotherapeutic methods which aim toward uncovering deeply repressed conflicts usually require a relatively long period of treatment in which the unconscious impulses, feelings, and thoughts are "teased out" into awareness very cautiously and slowly, so that no more anxiety is mobilized at any one time than the patient can tolerate. Patients requiring treatment of this type should be referred to psychiatrists who specialize in psychotherapy or psychoanalysis.

Case 11.—A 43-year-old married woman consulted one of us (J.S.G.) because of chronic urticaria which she had had for six months. One year previously she had undergone hysterectomy, and she was currently receiving injections from her family physician for menopausal symptoms. All the usual forms of treatment for urticaria had been exhausted by previous

physicians, including dermatological specialists. The past personal history revealed relatively good life adjustment except for divorce from her first husband and a short "nervous breakdown" in connection with that experience. She had remarried but had never quite recovered from the experiences surrounding her separation from the first husband. She was unable to discuss these incidents during the taking of the personal history. Because her illness was of relatively short duration and her psychological problems appeared to be rather recent in origin, this dermatologist decided to manage the case psychotherapeutically. Initially the patient was very constricted and distant during the interviews, but as time went on she became more relaxed and expressed confidence in the physician. She appeared to be burdened by some difficult problem which she could not bring herself to talk about. The physician had the impression that she was constantly on the verge of weeping but managed to choke back the tears. Without putting pressure on the patient to verbalize her burdensome problem to him, the physician gave her time to feel comfortable enough to discuss spontaneously. Eventually she told the details surrounding her divorce from the first husband, which involved a very disturbing period of wrangling over custody of the children. The husband had managed to obtain legal custody of the children because of the patient's illness at that time. As these incidents were recounted, the patient wept for the first time since the separation had occurred. After this interview her hives disappeared and did not return. Some time after treatment had been terminated, she phoned the physician to express her gratitude for his help and told him that the children had been returned to her.

This case illustrates that the dermatologist may often employ supportive psychotherapeutic methods safely and successfully and that in some instances he may profitably utilize mild ventilation and catharsis in connection with relatively recent or contemporary problems. He should not, however, strive primarily for the uncovering of unconscious material or the development of insight. In the present case, the patient's grief over loss of her children was not deeply repressed, but was very near the surface, and it was possible to help the patient psychotherapeutically by a kindly, permissive relationship in which she felt free to discharge some of these disturbing choked-up feelings.

SUMMARY

We answer the question, "Can the dermatologist do psychotherapy?" with a qualified "Yes." The important qualifications which we attach to our affirmative answer are specified and illustrated.

The qualifications for the dermatologist are that he must enjoy helping people, be able to sit quietly and listen comfortably, not become excessively anxious in doing this kind of work, be gratified and rewarded by his own life situation, and be relatively free from serious psychological problems in himself; he must have obtained training and supervision in dynamic psychiatry and psychotherapy.

The qualifications for the patient are that his illness is not too long-standing; the past history is one of relatively good social, occupational, marital, and sexual adjustment, and his emotional conflicts are primarily current. The patient to be treated by the dermatologist must not have psychoses, severe neuroses, or psychopathic disorders; he must not have delusions of parasitosis, acarophobia, long-standing atopic dermatitis, anal and genital pruritus syndromes, or dermatitis herpetiformis.

The qualifications for the psychotherapy are that it consist in supportive methods which reinforce mature aspects of behavior, promote organization and harmony, and strengthen the forces of repression. It may provide mild ventilation and catharsis in connection with current conflicts; it must avoid penetrating, excavating, extensively cathartic, and uncovering methods. The physician should not strive primarily for insight.

ALOPECIA AREATA

Prevalence in Japanese and Prognosis After Reassurance

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HONOLULU, T. H.

CELSUS said, "*alopekia* spreads out in a pattern where is pleases; but *ophiasis* [so called from its resemblance to a snake] begins at the back of the head [*ab occipitio*]," and these are the two kinds of baldness (*area*).[1] Perhaps this constitutes the first description of alopecia areata, but it is certainly not a very good one, and it may be that Kaposi was correct when he said that Celsus actually did not describe it at all.[2]

Celsus did very well, however, when he discussed treatment. He recommended scarification, painting with "resin of the turpentine tree," application of burned olive oil and "especially burned paper [*maximeque chartam combustam*]," and daily shaving. These suggestions have scarcely been deviated from, let alone improved upon, down to the present day.

The reason for the persistent popularity of such measures seems to have been, in general, their apparent effectiveness. The majority of patients recover within a reasonable period. Two recent reports, however, from Anderson in England [3] and Walker and Rothman in Chicago,[4] have indicated a rather poor outlook for recovery, especially in younger patients. The disparity between general experience (including my own) and these recent studies prompted, in large part, the investigation reported here. No extensive review of the literature or discussion of the moot question of etiology will be undertaken.

MATERIAL

A letter was written to each of 135 consecutive unselected patients with alopecia areata who were seen in my office from 1944 through 1950. Two statements were requested, as follows:

1. Hair all grew back in about.....weeks.

2. Further treatment was (needed, not needed). (Please underline one).

Very few of these patients had been seen more than once. For the majority of patients, no treatment was prescribed; the diagnosis was simply given and explained to the patient, together

Read before a staff meeting of the Straub Clinic, Honolulu, T. H., Nov. 5, 1951, and before the Hawaiian Academy of Science, Nov. 29, 1951.

1. Celsus, A. C.: De re medica, Lausanne, Haller, 1772, Bk. 6, Chap. 4; cited by Hebra, F., and Kaposi, M.: On Diseases of the Skin, Including Exanthemata, translated by C. H. Fagge and P. H. Pye-Smith, London, The New Sydenham Society, 1868, Vol. 2, p. 4.

2. Hebra, F., and Kaposi, M.: On Diseases of the Skin, Including the Exanthemata, translated by W. Tay, London, The New Sydenham Society, 1874, Vol. 3, pp. 206 ff.

3. Anderson, I. A.: Alopecia Areata: A Clinical Study, Brit. M. J. **2**:1250 (Dec. 2) 1950.

4. Walker, S. A., and Rothman, S.: Alopecia Areata: A Statistical Study of Endocrine Influences, J. Invest. Dermat. **14**:403 (June) 1950.

with a highly optimistic prognosis. For perhaps one-fifth of the patients, some placebo was prescribed, but its value and importance were always minimized, and no irritating preparation was used in any case. Eighty-four patients (62%) replied to the questionnaire.

AGE AND SEX INCIDENCE

The age distribution among the 135 patients whose cases were reviewed did not differ significantly from that of the population as a whole (Fig. 1). This is somewhat odd, in view of the fact that both Anderson in England and Walker and Rothman in Chicago found the age incidence to be almost the same in each of the first four decades, with a drop in the fifth.

Female patients outnumbered male patients by 78 to 57—the reverse of Sabouraud's findings in France some 30 years ago. However, women in Hawaii seldom wear hats; many of them never do, and it may be that this circumstance increases the cosmetic importance of the disease sufficiently to increase the proportion of women who complain of it here.

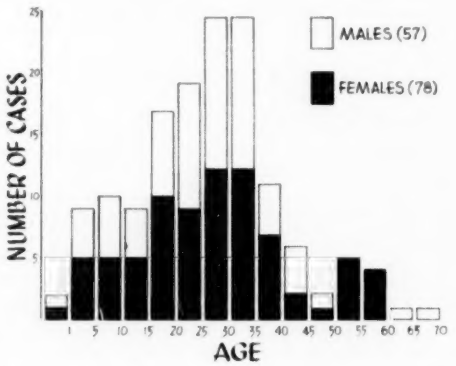

Fig. 1.—Number of cases according to sex among 135 consecutive patients with alopecia areata, by five-year age groups.

RACIAL INCIDENCE

Of the 135 patients, 82 (61%) were of Japanese ancestry. The rest were distributed among the other major racial groups in numbers too small to be significant. The difference between the proportion of Japanese in this series (61%) and the proportion of this racial group in my practice (35%) is statistically significant.

Additional evidence on this point has been obtained. In 1950 a morbidity survey was conducted by the Hawaii Chapter of the American College of Physicians. At its conclusion it covered 9,604 office diagnoses, 3,133 of them dermatological. In this group there were 69 diagnoses of alopecia areata, of which 38 (55%) occurred in Japanese, though this racial group comprised only 31% of the total. This difference too, I am informed, is statistically significant.

It is curious that not a single Filipino or Hawaiian, and only one part-Hawaiian, patient was seen in this series.

DURATION OF SYMPTOMS

Most patients were seen early in the course of their disease, before the end of the third month (Fig. 2). Two cases were of one year's duration; one was of two

years' duration, and one was of four years' duration. Eighteen patients must have had the symptoms for several months, at least, since they declined to estimate the duration of their condition.

PROGNOSIS

General Prognosis.—The great majority of the 84 patients who replied to the questionnaire reported regrowth of hair in three months or less, as shown in Figure 3. Only eight of this group reported that "further" treatment was required, and only nine of the remaining patients became sufficiently discouraged to go elsewhere (and were willing to admit it). Five patients, three of whom had sought further treatment, reported that their alopecia was still present after one year. Two reported recovery after one and one-half and after two years, respectively.

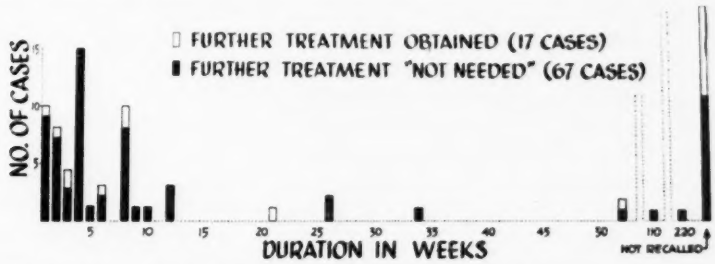

Fig. 2.—Duration of alopecia at time of first visit in 84 cases of alopecia areata, and number of cases in which "further" treatment was sought elsewhere.

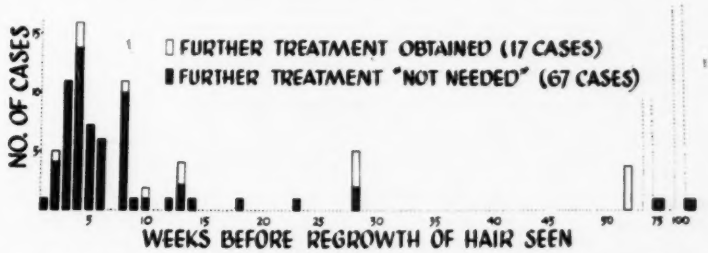
FURTHER TREATMENT OBTAINED (17 CASES)
FURTHER TREATMENT "NOT NEEDED" (67 CASES)
NO. OF CASES
WEEKS BEFORE REGROWTH OF HAIR SEEN

Fig. 3.—Weeks required for regrowth of hair following reassurance, with or without placebo medication, in 84 cases of alopecia areata. White bars indicate numbers of cases in which treatment was sought elsewhere.

Prognosis in Relation to Age.—For eight patients the age was not recorded. Of the remaining 76 patients (Fig. 4) only 11 reported that more than 15 weeks elapsed before "hair all grew back"; of these 11, only 4 were more than 25 years of age, but only 5 were under 15. It does not seem that the age distribution among these patients with the relatively stubborn disease, few as they were, differed from that of the group as a whole. Even the three patients whose alopecia was still present at the end of a year, and the one patient in whom regrowth of hair occurred only after two years, were scattered fairly uniformly between the ages of 10 and 50 years.

Prognosis in Relation to Duration of Symptoms When Seen.—Only 63 patients replying to the questionnaire had given the duration of their alopecia at the time

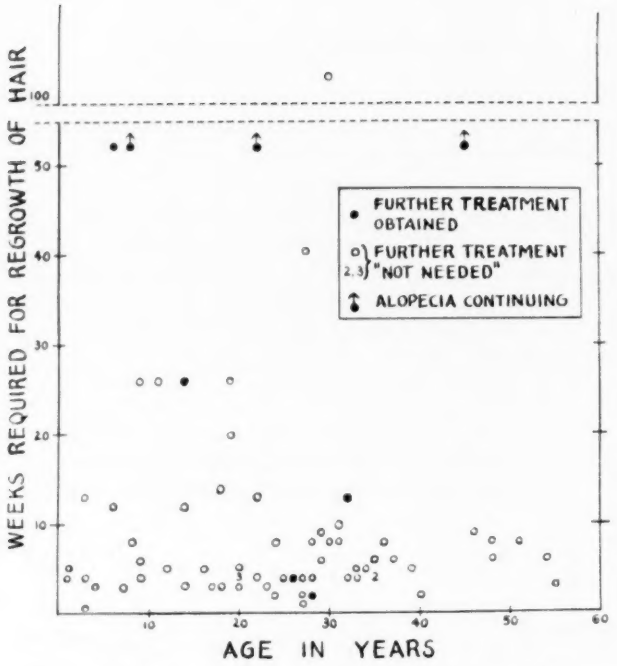

Fig. 4.—Prognosis of alopecia areata in relation to age in 76 cases.

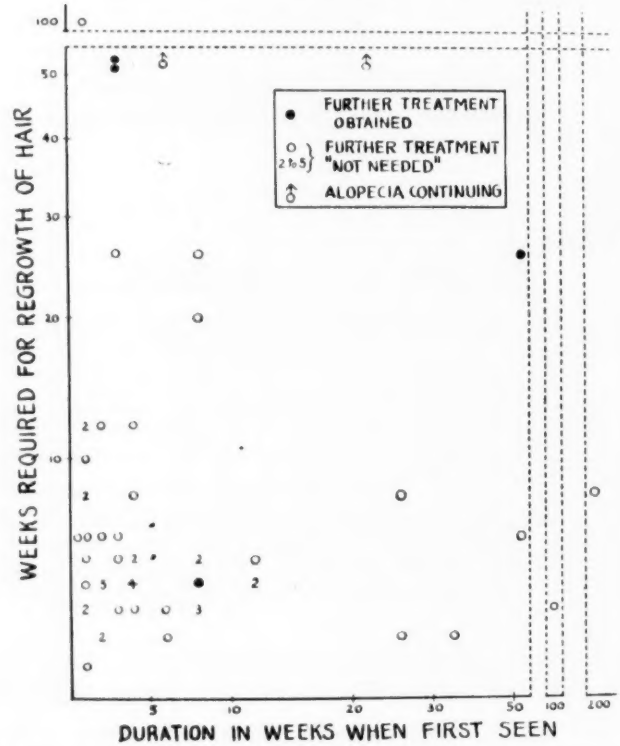

Fig. 5.—Prognosis of alopecia areata in relation to duration of symptoms when first seen, in 63 cases.

they were seen; in all except 8 of these the duration was under three months. Among these eight the duration was six months in three patients, eight months in one, a year in two, two years in one, and four years in one. Regrowth of hair occurred in less than 10 weeks in six of these eight patients; it required six months in one of the patients with alopecia of one year's duration (and the patient sought treatment elsewhere) and in one of those with six months' duration, alopecia was still present after a year (Fig. 5).

In the remaining 55 patients, those with alopecia of less than three months' duration, regrowth of hair was reported within three months or less in all but 7 patients, of whom 2 had sought treatment elsewhere and "achieved" success after one year; 4 had had regrowth of hair without "further" treatment after periods varying from 20 weeks to one year or (in 1 patient) two years; 1 reported continuing alopecia at the end of one year. It does not appear from these observations that the initial duration of symptoms influenced the eventual total duration of the disease.

COMMENT

Anderson, like Walker and Rothman, reported that alopecia persisted in about half of the younger patients—an observation which is at variance with the traditional observation of an increasingly poor prognosis with advancing years, with general experience, and with the observations on this series of patients. It seems possible that the ease of obtaining long follow-up studies on persistent cases, and the comparative difficulty of following those in which recovery is rapid, may have some bearing on the discrepancy.

The age incidence in this series corresponds to that given by Kaposi; that is, the disease occurred with roughly equal frequency at all ages, with the great majority of patients in point of numbers being affected between the ages of 15 and 35. This stands in sharp contrast, again, to the observations of the authors cited above, both of whom found their patients divided almost equally by decades up to the age of 30 or 40.

The effect of treatment has never been assessed, so far as I can learn; dermatological authors, almost to a man, from Celsus through Bateman [5] to the moderns, warmly recommend topical irritation of the affected areas. George Henry Fox [6] alluded to the fact that "hair may grow again, in some cases, even without treatment." Sequeira, however, though in his third edition [7] he had recommended the usual treatment, in his fifth edition,[8] coedited by Ingram and Brain, stated that "treatment makes little difference in the course" and assigned only secondary value to local stimulation and irritation.

Sequeira, Ingram, and Brain assigned first importance to the relief of emotional stresses and strains, mild sedation, and "general measures." Andrews [9] recom-

5. Bateman, T.: A Practical Synopsis of Cutaneous Diseases, Ed. 2, Philadelphia, Collins & Croft, 1818.

6. Fox, G. H.: Photographic Illustrations of Skin Diseases, New York, E. B. Treat & Company, Inc., 1880.

7. Sequeira, J. H.: Diseases of the Skin, Ed. 3, Philadelphia, P. Blakiston's Son & Co., 1919.

8. Sequeira, J. H.; Ingram, J. T., and Brain, R. T.: Diseases of the Skin, Ed. 5, New York, The Macmillan Company, 1947.

9. Andrews, G. C.: Diseases of the Skin, Ed. 3, Philadelphia, W. B. Saunders Company, 1946.

mended, but with skepticism, irritants and ultraviolet irradiation and stated that rest and a high-caloric diet are important. Sutton [10] emphasized the frequency with which the onset of baldness coincides with death in the family, a business failure, a divorce, or "working the night shift" and suggested that abscessed teeth or infected tonsils may also be implicated. Haynes and Parry [11] believed refractive errors are of major importance and reported in most cases regrowth of hair in three months following correction of these.

It is interesting to note that the most optimistic prognosis by far among these authors (that of recovery in three months, by Haynes and Parry, or in two to four months, by Sequeira, Ingram, and Brain) is given by the very authors who assign the least value to topical medications. It is a familiar observation in the management of psychogenic complaints generally that medical or surgical treatment may make it more difficult to get rid of them; it is tempting to postulate that giving these complaints much serious attention or vigorous pharmaceutical treatment lends them, in the patient's eyes, a certain "element of value" in that they gain for him attention and sympathy.

On the long-popular hypothesis [12] that alopecia areata is a response to stress, usually emotional stress, one might then argue that the prognosis would be improved, other things being equal, by belittling the disorder, by paying it the least possible attention, by not treating it, but by merely giving an optimistic prognosis and letting the patient alone.

This is just what has been done in this series of patients, and it would appear that the results justify this approach.

CONCLUSIONS

Alopecia areata is disproportionately prevalent among Japanese in Hawaii.

The age distribution of patients with alopecia areata in Hawaii does not appear to differ from the age distribution of the general population; patients seem equally susceptible at all age levels.

Female patients with the disease outnumber male patients in a ratio of approximately 4:3.

The prognosis of alopecia areata following reassurance and the giving of an optimistic prognosis to the patient is good for recovery within three months and excellent for recovery within a year. This prognosis seems at least as good as that following treatment, if not better. It seems unrelated to the previous duration of symptoms and to the age of the patient.

It is suggested that the best treatment for alopecia areata may be simple reassurance.

Mr. Melville Taff, Chief of the Bureau of Health Statistics, Hawaii Territorial Department of Health, evaluated the data relating to frequency of occurrence of the disease in the Japanese.

1020 Kapiolani St. (14).

10. Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949.

11. Haynes, H. A., Jr., and Parry, T. L.: Alopecia Areata Associated with Refractive Errors, Arch. Dermat. & Syph. **59**:340 (March) 1949.

12. Gaucher, E.: Traité des maladies de la peau, Paris, Octave Doin, 1895. Robinson, S. S., and Tasker, S.: Alopecia Areata Associated with Neurodermatitis, Urol. & Cutan. Rev. **52**:467 (Aug.) 1948. Barber, H. W.: Psoriasis, Brit. M. J. **1**:219 (Jan. 28) 1950. Anderson.[8] Sequeira and others.[8] Sutton.[10]

HYPOTHYROIDISM, LIVER DAMAGE, AND VITAMIN A DEFICIENCY AS FACTORS IN HYPERKERATOSIS

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THE SYNDROME of carotenemia, which was first described by von Noorden in 1907,[1] has been observed in a variety of metabolic disorders, including diabetes mellitus, chronic glomerulonephritis, myxedema, acute hepatic disease, xanthomatosis, and the ingestion of unusual quantities of vegetables rich in carotenoid pigments.

Carotene is not synthesized by man. The absorption of carotene and its biologically active form, vitamin A, from the small intestine is linked with the absorption of lipids, is enhanced by the presence of lecithin, and, in the case of carotene, is dependent on the presence of bile salts. About 30 to 50% of the ingested carotene is converted to vitamin A,[2] and in man both conversion and storage take place in the liver.[3] Mattson and associates have demonstrated that conversion in rats takes place chiefly in the intestinal mucosa.[4] Because carotenemia usually occurs in association with diseases of the liver and thyroid gland, it has been suggested that the metabolism of carotene is dependent on the integrity of these organs.[5]

Several cases of carotenemia in association with myxedema have been reported by Escamilla[6] and by Mandelbaum,[7] in which the carotenemia disappeared with the administration of thyroid extract. Clausen and McCoord noted high plasma carotene levels and, more commonly, low plasma vitamin A levels in the majority

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1. von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, Ed. 4, Berlin, A. Hirschwald, 1907, p. 382.

2. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, Ed. 4, Toronto, Canada, University of Toronto Press, 1946, p. 636.

3. Moore, T.: Vitamin A and Carotene: The Distribution of Vitamin A and Carotene in Body of the Rat, Biochem. J. **25**:275, 1931. Drummond, J. C., and MacWalter, R. J.: The Fate of Carotene Injected into the Circulation of the Rat, J. Physiol. **83**:236, 1934.

4. Mattson, F. H.; Mehl, J. W., and Deuel, H. J., Jr.: Studies on Carotenoid Metabolism: The Site of Conversion of Carotene to Vitamin A in the Rat, Arch. Biochem. **15**:65, 1947.

5. Anderson, H. H., and Soley, M. H.: The Effects of Carotenemia on the Function of the Thyroid and the Liver, Am. J. M. Sc. **195**:313, 1938.

6. Escamilla, R. F.: Carotenemia in Myxedema: Explanation of the Typical Slightly Icteric Tint, J. Clin. Endocrinol. **2**:33, 1942.

7. Mandelbaum, T.; Candel, S., and Millman, S.: Hypothyroidism, Hyperlipemia and Carotenemia, J. Clin. Endocrinol. **2**:465, 1942.

of the cases of hypothyroidism they studied.[8] These facts seem to indicate that the hypofunctioning thyroid gland retards the utilization of carotene. Laboratory work appears to support this conclusion. Drill produced vitamin A deficiency in thyroidectomized rats on a vitamin-A-free diet and receiving injections of carotene.[9] Xerophthalmia has been noted in thyroidectomized rabbits on a diet of sufficient carotene content for normal animals of the same species.[10] Johnson and Baumann observed that, when given equivalent amounts of carotene, hyperthyroid rats accumulated much larger liver stores of vitamin A than did normal rats.[11] Although the available evidence indicates that carotene is not metabolized to vitamin A in the absence of thyroid function, the manner in which the thyroid gland acts on carotene has not been elucidated.

The effects of vitamin A deficiency upon the human skin are well known and are characterized by hyperkeratinization. Frazier and Hu described the typical lesions as consisting of grouped follicular papules with a central keratotic plug or spine.[12] Fasal described severe cases in which large papules, flat or hemispherical, occasionally acneiform or resembling lichen planus, were present.[13] The anterolateral aspects of the thighs and the posterolateral aspects of the upper arms are often the first sites of localization, and the condition may then spread to the extensor surfaces of the arms, legs, buttocks, shoulders, and abdomen. Diffuse branny scaling of the skin and inhibition of sweat and of sebaceous secretion may be noted. Dryness and brittleness of the hair and brittleness of the nails may be present. The skin symptoms usually precede the ophthalmic symptoms.

Because of the curious relation of the thyroid gland to carotene and vitamin A, the following case appears worth reporting.

REPORT OF A CASE

A 61-year-old housewife was first seen in November, 1944, complaining of fatigue, dyspnea, intolerance to cold, and stiffness of the hands and feet of one year's duration. For three months she had noted hardening of the palms and the soles. There was a family history of diabetes mellitus. She was pale, stout, and apathetic and had been taking an iron preparation for anemia.

A soft apical systolic murmur was present, and her deep reflexes were decreased. The pulse rate was 76, and the blood pressure was 150/76. The skin was of faint yellowish tinge and very dry throughout; on the back and on the extensor surfaces of the upper arms and thighs, a fine, branny desquamation was noticeable. The inner and the posterolateral aspects of the thighs showed numerous follicular keratotic lesions, without any perifollicular erythema. Some of these follicular cones showed thin, horny spines of 2- to 3-mm. length (Fig. 1). Palms and soles showed a diffuse yellow transparent keratosis, and in the center of the palms and soles areas of dark brownish fissured keratoses were present (Fig. 2). Below and on the ankles and

8. Clausen, S. W., and McCoord, A. B.: The Carotenoids and Vitamin A of the Blood, J. Pediat. **13**:635, 1938.

9. Drill, V. A., and Truant, A. P.: Effect of Thyroidectomy on the Conversion of Carotene to Vitamin A, Endocrinology **40**:259, 1947.

10. Kunde, M. M.: Studies on Experimental Cretinism: III. Nutritional Disturbances, Pellagra and Xerophthalmia, Proc. Soc. Exper. Biol. & Med. **23**:812, 1926.

11. Johnson, R. M., and Baumann, C. A.: The Effect of Thyroid on the Conversion of Carotene into Vitamin A, J. Biol. Chem. **171**:513, 1947.

12. Frazier, C. N., and Hu, C. K.: Cutaneous Lesions Associated with Deficiency in Vitamin A in Man, Arch. Int. Med. **48**:507, 1931.

13. Fasal, P.: Cutaneous Diseases in the Tropics: Clinical Study Based on Observations in Malaya, Arch. Dermat. & Syph. **51**:163, 1945.

Fig. 1.—Follicular keratotic and spinular lesions on thighs and keratotic psoriasiform plaques on knees.

Fig. 2.—Keratosis palmaris.

on the lower legs were numerous flat papular and patchy keratotic lesions, resembling patches of lichenified dermatitis, but erythema and pruritus were absent (Fig. 3). On the chest and the back were numerous seborrheic warts, characteristic on the chest but showing much keratosis on the back and resembling senile keratomas.

Histological examination showed hyperkeratosis as the main feature and some acanthosis, with little lymphocytic infiltration in the cutis.

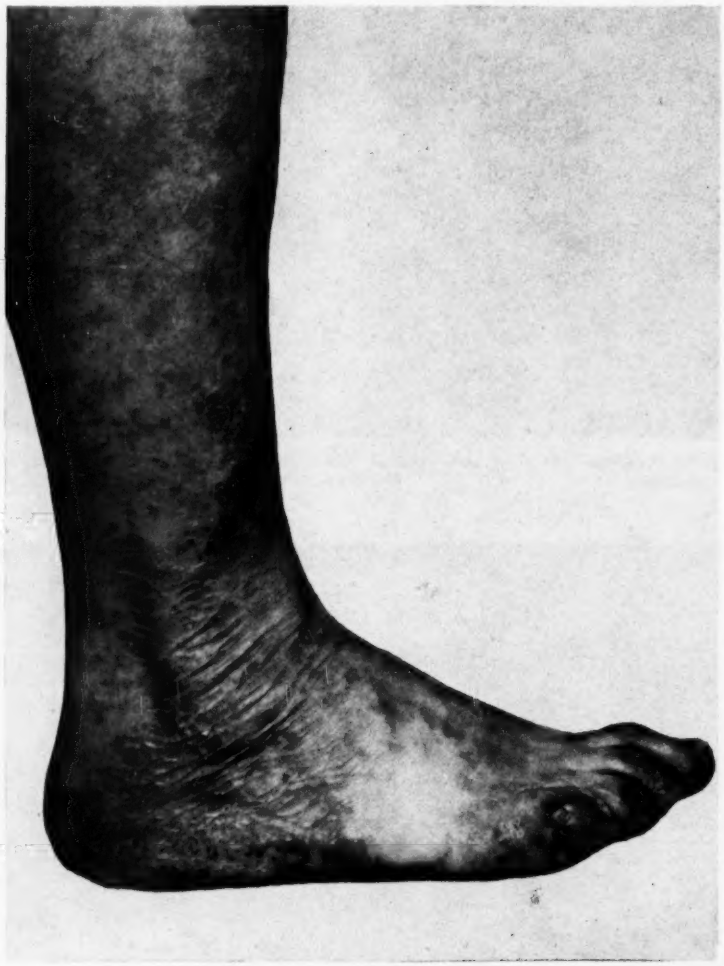

Fig. 3.—Flat keratotic papules on leg and diffuse keratosis on heel.

The nails and the mucous membranes were normal. Urinalysis disclosed no abnormality. The hemoglobin concentration was 69%. There were 5,700 white blood cells with 70% polymorphonuclear cells, 2% eosinophiles, 6% monocytes, and 22% lymphocytes. The sedimentation rate was 18 mm. per hour (Wintrobe). The Wassermann reaction was negative. The direct-reacting bilirubin was 0.43 mg. per 100 cc., or 33% of the total bilirubin, which was 1.3 mg. per 100 cc. Sulfobromophthalein (bromsulphalein®) sodium retention was 18.6% after one-half

hour. Hippuric acid synthesis was 0.440 gm. in one hour. The basal metabolic rate was —30%, and the serum cholesterol was 232 mg. per 100 cc. The total serum proteins were 7.54 gm. per 100 cc.; the albumin was 4.93 gm. and the globulin 2.61 gm.

The chest roentgenogram was normal; the electrocardiogram showed a left axis shift, with low voltage QRS complex and inverted T wave in Leads I and II and diphasic T wave in Lead CF_4.

The dietary intake for previous months had been adequate in all vitamins.

Vitamin	Intake per Day (Calculated from Diet by Dietitian)	Normal Values per Day
A (preformed)	17,246 I. U.	5,000 I. U.
B_1	1.5 I. U.	1.2 I. U.
B_2	1.6 I. U.	1.8 I. U.
C	94 mg.	70 mg.

A vitamin A absorption curve after administration of 250,000 units of vitamin A (given by mouth in form of percomorph liver oil showed the following serum values:

	Carotene, Mg./100 Cc.	Vitamin A
Before meals	0.46	97.5 I. U.
Normal values before meals	0.08 to 0.23	80.0 to 190.0 mg./100 cc.
5 hr.	0.44	102.0 I. U.
7 hr.	0.44	130.0 I. U.
Normal values after meals	....	350.0 to 650.0 mg./100 cc.

The fasting vitamin A level was within normal limits, but the slow and incomplete rise showed impaired absorption of orally taken vitamin A.

Treatment was started with 0.13 gm. of thyroid three times a day, and vitamin A, 500,000 units three times a day.

In January, one month after her discharge from the hospital, the patient's symptoms had decreased, and after three months' treatment her palms and soles were entirely clear, and the lichen spinulosus had vanished without a trace. The fatigue and cold intolerance had disappeared, her weight had increased, her blood pressure had risen to 180/90, her hemoglobin concentration was 90%, and the basal metabolic rate was +24%. Results of liver-function tests improved later, and the carotenemia disappeared. The fasting vitamin A level had been normal or low normal throughout. The vitamin A-tolerance curve, which had been flat at first, was normal one year after therapy was instituted (Table). It is of interest to note that in 1949, five years after cure of the symptoms described, the patient had a macrocytic anemia responding to liver therapy.

COMMENT

The patient's clinical condition and low basal metabolic rate were conclusive evidence of hypothyroidism. The electrocardiographic findings, blood cholesterol level, and anemia supported this diagnosis. That there was some liver dysfunction was indicated by the slightly elevated bilirubin level, impaired hippuric acid synthesis, and sulfobromophthalein sodium retention. However, the last two determinations must be viewed with reserve since the hippuric acid synthesis may have been decreased by the anemia, and the sulfobromophthalein sodium retention may have been affected in part by the elevated bilirubin and carotenemia. Unfortunately, in this case there was no test for night blindness.

The lichen spinulosus on the thighs may be considered as a typical lesion of vitamin A deficiency. The flat papular and patchy keratosis on and about the ankles has been described as occurring in such cases [13] but is rarely seen outside the tropics.

The palmar and plantar keratosis was extremely unusual. The clinical impression was that of a keratosis palmaris et plantaris as seen as an expression of nevoid genodermatosis, and only the effect of vitamin A therapy proved that this disorder also formed part of the avitaminosis. Other stigmata of vitamin A deficiency, such as Bitot's spots, xerophthalmia, and keratomalacia, which are signs of advanced deficiency, were not present in this case. It may be that the dry skin of myxedema is a predisposing factor for the keratotic changes associated with vitamin A deficiency.

The carotenemia was interpreted as evidence of decreased utilization of carotene by the liver and decreased synthesis of vitamin A. Since carotenemia and vitamin A deficiency occasionally complicate liver disease, the impairment of carotene metabolism may have been accentuated by the liver damage present. The skin lesions disappeared, and the serum carotene level became normal on therapy with thyroid

Summary of Laboratory Findings on a Patient with Hyperkeratosis

Date	Basal Metabolic Rate, %	Bilirubin, Mg./100 Cc. Direct	Bilirubin, Mg./100 Cc. Total	Sulfobromophthalein Retention, %	Hippuric Acid Synthesis, Gm.	Total Proteins, Gm./100 Cc.	Hemoglobin, %	Serum Cholesterol, Mg./100 Cc.	Carotene, Mg./100 Cc.	Vitamin A, I. U.
Nov., 1944	— 20	0.43	1.3	18.6	0.440	7.54	69	232	0.46	97.5 a. c.* 102 p. c. (5 hr.†) 130.0 p. c. (7 hr.†)
Feb., 1945	+ 24	0.25	0.65	10.4	.....	....	90	231	0.13	194.7 a. c.
May, 1945	— 4	0.25	0.75	14.1	1.054	6.88	80	267	0.143	250.1 a. c.
July, 1945	.....	0.45	0.95	5.4	.....	8.41	80	267	0.185	164 a. c.
Nov., 1945	+ 7	0.9	2.2	6.25	.....	7.28	100	225	0.125	168 a. c. 595 p. c. (5 hr.†)
Dec., 1948	+ 1	1.3	2.2	7.6	.....	7.03	85	218	....	.....

* A. c. (ante cibum) is before meals; p. c. (post cibum) is after meals.
† Time after ingestion of 250,000 units of percomorph liver oil.

extract, suggesting that this hormone is necessary before carotene can be metabolized in the usual manner. Although vitamin A was given simultaneously, its previously high dietary intake indicated that the main therapeutic effect was from thyroid extract.

Because the vitamin A-tolerance curve was flat, it appears that there was either a decreased absorption of vitamin A from the small bowel or a period during which depleted liver stores of vitamin A were replenished at the expense of serum levels. Since the intake of vitamin A previous to treatment was high, we are inclined to believe that the flat vitamin A-tolerance curves were due, in part at least, to decreased intestinal absorption. Popper and his associates,[14] noting such tolerance curves in patients with liver disease without jaundice, concluded that they were due to poor intestinal absorption of vitamin A, perhaps because of the lack of some bile acid.

We can only speculate on the reason this patient's liver-function-test reactions returned to normal on therapy with thyroid extract. Escamilla reported a case of

14. Popper, H.; Steigmann, F., and Zevin, S.: On the Variations of the Plasma Vitamin A Level After the Administration of Large Dosages of Vitamin A in Liver Disease, J. Clin. Invest. **22**:775, 1943.

hepatic dysfunction and carotenemia in association with hypothyroidism which showed improvement of hepatic function on similar therapy.[6] His suggestion that liver function may be depressed by lowered metabolism seems to apply here.

SUMMARY

A case of hypothyroidism in association with carotenemia, vitamin A deficiency with widespread keratoses, and impaired liver function is presented.

Liver function improved, the carotene level in the blood decreased, and the keratoses disappeared permanently on therapy with vitamin A and thyroid extract. Because the vitamin A content of the pretherapy diet had been more than adequate, it was thought that the main therapeutic effect was due to thyroid extract.

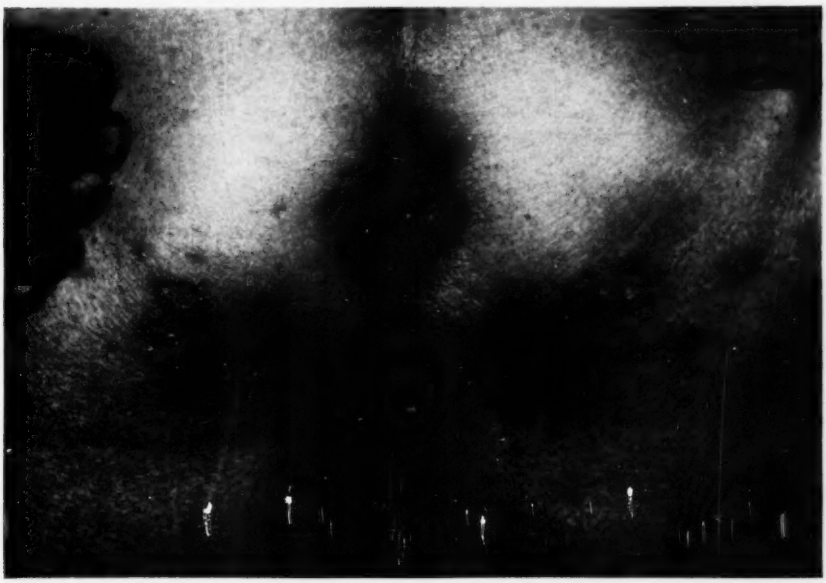

Fig. 4.—Keratotic lesions on buttocks and on hemorrhoidal tags in a man with myxedema.

It is suggested that the vitamin A deficiency was due both to decreased intestinal absorption of vitamin A and to a decreased synthesis of vitamin A from carotene in the liver.

ADDENDUM

The combination of hypothyroidism and lack of vitamin A may not be a too-rare event. We saw lately a 60-year-old male patient having a fully developed myxedema with macroglossia who showed widespread keratotic lesions, chiefly localized on the knees, elbows, buttocks, and hemorrhoidal tags (Fig. 4). A low vitamin A level was found in his serum in spite of adequate dietary intake. The lesions disappeared with thyroid and vitamin A medication.

Suite 613, 1414 Drummond St. (Dr. Kalz).

SOLITARY CONGENITAL NODULAR CALCIFICATION OF THE SKIN

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SOLITARY congenital nodular calcification of the skin is a form of calcinosis circumscripta. I have been unable to find a description of this condition in the literature. This unusual clinical and histopathological condition was observed in three instances.

REPORT OF CASES

CASE 1.—J. S., a 28-month-old boy, was seen Aug. 12, 1946, for an apparent cystic nodular lesion 3 mm. in diameter involving the eponychium and posterior nail wall of the right index finger. It had been present since birth and had grown very slowly. There was no inflammatory reaction evident clinically. With the area under local anesthesia, the skin bordering the lesion was incised and the nodule curetted out.

The hematoxylin-eosin-stained histologic section of the curetted specimen showed hyperkeratosis and acanthosis of the epidermis. Directly beneath the epidermis were irregular amorphous masses of basophilic calcium.

CASE 2.—E. R., a 13-month-old girl, had a lesion on the left sole since birth. Clinically it appeared to be either a plantar verruca or a callous formation. It had been treated previously for these conditions without effect. On June 26, 1951, with the area under local anesthesia, the lesion was removed with a 4-mm. cutaneous punch. The incision was closed by one dermal suture, and the site healed by primary intention.

Microscopic examination of the hematoxylin-eosin-stained section of the removed specimen showed the epidermis to be acanthotic and covered by hyperkeratotic stratum corneum. Directly beneath the epidermis was a lobulated calcified deposit in the cutis. This bluish, calcified material was observed to extend through the epidermis into the stratum corneum, localized to the site of the sweat pore and duct. No epithelial lining or inflammatory reaction was observed surrounding the amorphous calcified masses. A section stained for elastic tissue showed no such tissue in the cutis adjacent to the calcified masses.

CASE 3.—M. R., a 10-month-old girl, was seen Aug. 21, 1951. She had a nodular lesion 4 mm. in diameter on the inner right knee. This nodule began at birth as a pinhead-sized white papule which gradually became larger. It was reddish-yellow and clinically appeared to be either a xanthoma or an epidermal cyst. The lesion was excised, and a specimen was sectioned and examined microscopically.[1]

The hematoxylin-eosin-stained section showed that the epidermis was acanthotic. Underneath the acanthotic epidermis were cystic areas lined by a single layer of epithelium. These cysts contained amorphous as well as spherical masses of calcium. In some areas the retaining wall of epithelium had disappeared. The section stained for elastic tissue showed normal elastic tissue throughout the entire cutis.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Dr. Paul LeVan furnished the histologic specimen from this patient.

HISTOLOGIC OBSERVATIONS

There is a similarity in the histologic appearance of the lesion in Case 3 to epithelioma adenoides cysticum (Brooke's disease) and also to calcifying syringoma. In areas the surrounding epithelium has disappeared, and the nests of calcium lie free in the upper cutis adjacent to the epidermis. Thus, the histologic section of Case 3 resembles that seen in Cases 1 and 2. In Case 2 the histologic picture at first glance suggests a verruca vulgaris, as did the clinical examination. This is because of the arborization of the adjacent epidermal pegs. However, the degenerated epidermal cells seen in verruca vulgaris and verruca plantaris are not

Fig. 1 (Case 1).—Photomicrograph of curetted specimen showing hyperkeratotic and parakeratotic epidermis overlying nests of calcium in papillary cutis; × 60.

evident; therefore, we cannot consider this a verruca histologically. In none of the sections stained for elastic tissue could such tissue be seen in the calcified masses.

The youngest patient (Case 3), aged 10 months, had lesions which were surrounded by epithelium. The second patient, aged 13 months, had a lesion which histologically not only was localized in the cutis but could be observed in the sweat pore of the epidermis and stratum corneum, whereas the oldest patient, aged 28 months, was observed to have this calcium without any relation to a preexisting adnexal structure. It seems that the epithelium which lines the periphery of the lesion in its earliest stages becomes absorbed as time goes on.

COMMENT

Calcification in the skin is of two types: (1) the localized and (2) the generalized. The generalized form of skin calcification is divided into two types, the metabolic and the metastatic. The metabolic type includes those cases in which calcium is present in the tissues because of a metabolic or endocrine gland disturbance as well as because of debilitating diseases, such as dermatomyositis, sclero-

Fig. 2.—Same as Figure 1, except higher magnification. Amorphous calcified dark-staining masses in papillary cutis without any adjacent inflammatory reaction; × 110.

derma, and Raynaud's disease. The metastatic form of generalized calcification seen in osteomyelitis, lymphatic leukemia, kidney disease, etc., is characterized by decalcification of bone with a simultaneous demonstrable increase in blood calcium. In the metabolic type of calcification, Weidman and Shaffer [2] were able to find calcium in all structures except sebaceous glands. They observed the similarity

2. Weidman, F. D., and Shaffer, L. W.: Calcification of the Skin Including the Epiderm in Connection with Extensive Bone Resorption, Arch. Dermat. & Syph. **14**:503-532, 1926.

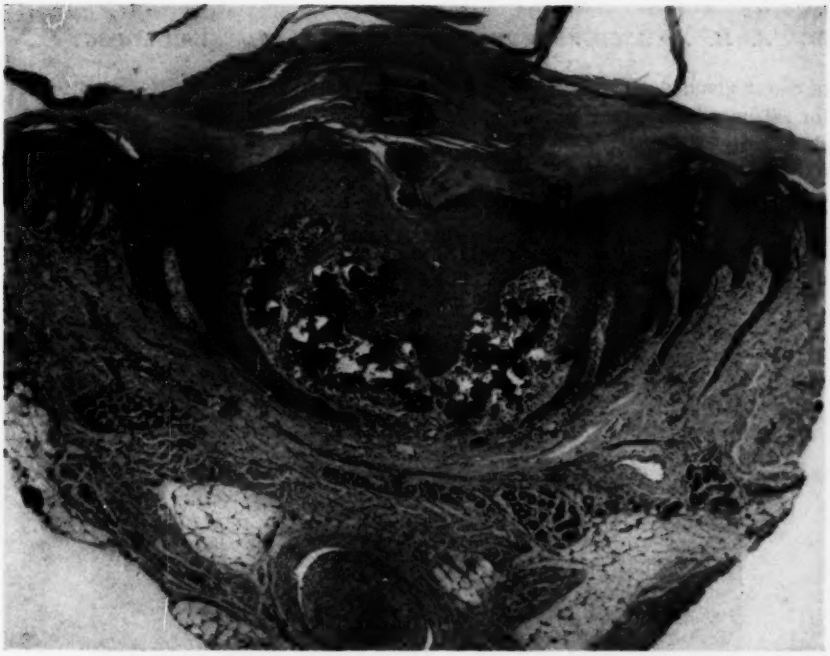

Fig. 3 (Case 2).—Photomicrograph showing parakeratotic and hyperkeratotic stratum corneum containing nests of calcium which extend down through sweat pore toward rete. Papillary cutis shows irregular masses of calcified material with arborization of adjacent epidermal pegs. Absence of inflammatory reaction in cutis; × 60.

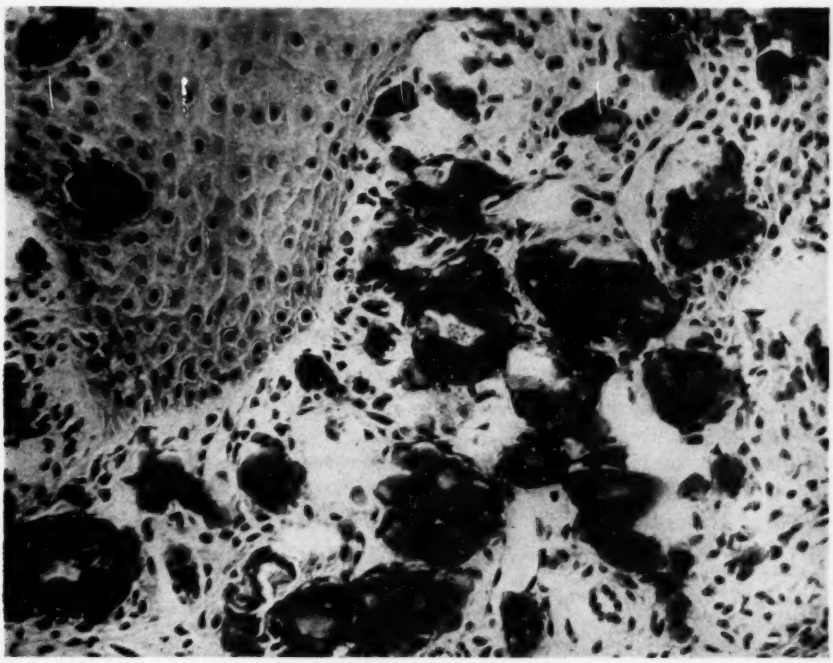

Fig. 4.—Same as Figure 3. Photomicrograph showing calcium in irregular clumps and masses in cutis and some lying in epidermis; × 110.

of sweat gland ducts to the tubules of the kidney in that both were favorite sites for calcium deposits and noted that these, together with the lungs, were the three acid-excreting organs of the body.

The patients with localized form of calcification of the skin do not have an associated increase in blood calcium. Calcification in these patients is due to a deposition of calcium in tumors, as epitheliomas, epidermal cysts, dermal cysts, or

Fig. 5 (Case 3).—Photomicrograph showing deeper-lying cysts containing calcium in irregular amorphous masses. Epidermis appears acanthotic. There is no inflammatory reaction in cutis, nor can any foam cells be observed; × 60.

atheromas, in chronic inflammatory granulation tissue, such as that of tuberculosis, and in dystrophically changed tissue, such as that of pseudoxanthoma elasticum.

Kerl [3] stated that Aschoff believed that calcium was deposited because of a strong calcium affinity of the albumin bodies formed as a result of abnormal metabo-

3. Kerl, W.: Beiträge zur Kenntnis der Verkalkungen der Haut, Arch. Dermat. u. Syph. **126**:172-251, 1919.

lism. Heile,[4] in his studies on ochronosis and pseudoxanthoma elasticum, stated that elastic fibers have an affinity for calcium and iron.

Kerl [5] believed that this type of calcification was the result of local asphyxia or a reduction in the local metabolism. Doessekker [5] stated that calcium deposition is based on degeneration products, since, as a rule, all tissues having scanty nutri-

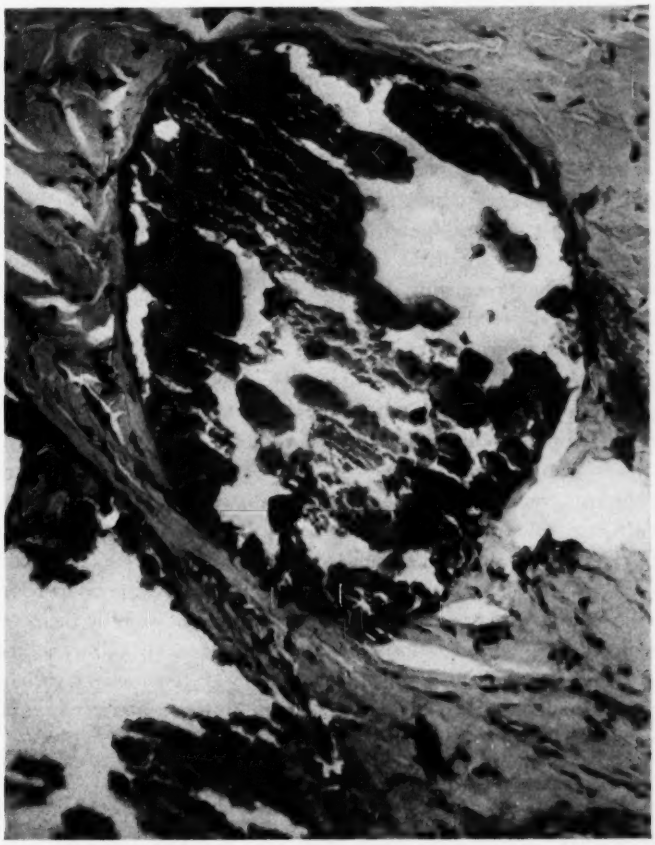

Fig. 6.—Higher magnification of area of Figure 5 shows calcified masses in some areas surrounded by single layer of residual epithelium; × 110.

tion or reduced metabolism undergo petrifaction. Therefore, a calcified cell is not necessarily a dead cell. McGowan [6] proposed that in the process of necrobiosis

4. Heile, D.: Ochronosis and Pseudo-Ochronotic Pigmentation of Cartilage, Arch. path. Anat. **160**:148-173, 1900.

5. Doessekker, K.: Beitrag zur Kenntnis der Kalkablagerungen mit spezieller Berücksichtigung der sog. verkalkten Epitheliome der Haut, Arch. Dermat. u. Syph. **129**:260-298, 1921.

6. McGowan, J. P.: Calcification, Brit. M. J. **2**:895, 1933.

of the cells, the phospholipins are broken up, giving rise to free phosphoric acid which, having been neutralized by calcium of the blood, appears as deposits of calcium phosphate. He backed this up with the fact that in rickets there is a deficiency of phospholipins and of phosphate in the body generally, and by the belief that vitamin D mobilized the phosphate from the body tissues into the blood stream. Costello[7] believed that calcification in infants was the result of subcutaneous fat necrosis.

Elastic fibers have a great affinity for calcium deposition,[8] especially when they undergo degeneration. The calcium covering these elastic fibrils assumes the wavy outline of the underlying elastic fibrils. Thus, calcium deposits in the form of sheets may be found as focal concretions within the connective tissue, although no inflammatory reaction is present. Calcium salts found are calcium carbonate and calcium phosphate. At times, these salts are combined with a trace of magnesium. In contrast to those found in gout, these calcium deposits contain no uric acid. Therefore, the nature of the calcification in the localized or generalized types is dependent on the preexisting lesions. The epidermis overlying the calcium deposition undergoes secondary changes, such as scaling, reddening, crust formation, and even tumor formation.

The pathogenesis of calcium deposits is dependent on the local changes in the tissues and the presence of calcium in the blood stream. It seems that reduced tissue vitality is a predisposition for the tissue affinity toward calcium salts. Necrosis, such as is seen in caseation necrosis of tuberculosis or mortified granulation tissue, atheromas, or similar nonvital structures, such as keratin and dystrophic connective tissue, offer sites for calcium deposition. These forms of calcification have been classified as localized calcinosis or pseudocalcinosis by Aschoff.[9] Degenerated tissue has the same affinity for calcium as does the previously mentioned elastic tissue. Vitamins have been known to cause calcification by their local action on cutaneous lesions.[10] Necrobiosis and senile changes, as well as lesions associated with excessive production of carbon dioxide or retention of carbon dioxide due to faulty circulation, are considered by some to cause precipitation of calcium in the tissues.

SUMMARY

In the three patients studied, it appears that the predisposing skin condition was a hamartoma of sweat duct origin, most likely a syringoma, the cystic contents of which were calcified. Subsequently the limiting epithelial membranes were absorbed, and the free-lying masses were seen in the cases of longer duration. The spherical configuration of the calcium deposits, the localization near and in

7. Costello, M. J.: Cutaneous Calcinosis, New York J. Med. **35**:1266-1271, 1935.

8. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, Vol. 1, pp. 147-152.

9. Aschoff, cited by Kerl.[8]

10. Juster, M., in discussion on Gougerot, H., and Burnier: Concrétions calcaires isolées et symétriques des cuisses, Bull. Soc. franç. dermat. et syph. **42**:426-429, 1935.

the epidermis, the occurrence at the sites of sweat ducts and sweat duct pores indicate this most likely to be a calcification of a hamartoma of sweat gland origin.

CONCLUSION

Three cases are presented of localized nodular congenital calcinosis of the skin in clinical lesions which appeared as cystic (Case 1) and verrucous or calloused (Case 2) lesions and as a fibroxanthoma (Case 3). All cases histologically were characteristic of calcification.

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Photomicrographs were supplied by William M. L. Martinsen, F.B.P.A.

NOMENCLATURE, CLASSIFICATION, AND PATHOGENESIS OF "ECZEMA" IN INFANCY

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WHAT is called "eczema" in infants is, just as in adults, a group of various dermatoses which sometimes closely resemble one another. Infants have atopic, contact, seborrheic, and infectious eczematoid dermatitis, eczema-like fungous infections, nummular eczema, and eczematoid eruptions which do not fit into any of these categories and are impossible to classify.

CLASSIFICATION AND NOMENCLATURE

It has been said that 75% of "eczema" in infancy is atopic dermatitis. A few weeks ago records from my files of 100 patients under 2 years of age were tabulated, and it was found that the diagnosis of atopic dermatitis had been made for 69, and that of contact dermatitis for 13, while the remaining 18% of the group had other dermatoses. I will confine my remarks almost entirely to atopic dermatitis.

About 7% of the population differ from the rest in their immunological response to natural exposure by ingestion or inhalation of foreign protein. They become easily sensitized and have hay fever, asthma, or dermatitis as the commonest manifestations of such sensitization. They are called "atopic" by many allergists and by some dermatologists, and, if this nomenclature is used, it is fitting to call the dermatitis they have "atopic dermatitis." They show multiple positive skin tests of the immediate urticarial type and often have circulating antibodies which can be transferred to the skin of a normal person. This perversion, this distortion of immunology, which is perhaps best looked upon as an exaggeration of the normal, is to a considerable extent determined by heredity. Of the 69 infants with atopic dermatitis already mentioned, 18 of the parents had hay fever, and 7 had asthma.

Although it has been called by different names at different age periods, atopic dermatitis is the same disease at all ages, and it seems best to call it by the same name at all ages, because it is as much a definite constitutional disease as is diabetes or epilepsy and it may last from early infancy to middle age. Only in infancy has this disease been called "eczema" by the European school of dermatology, because in infancy spongiosis, intraepidermal vesiculation, and consequent oozing are not uncommon; later, when the morphology has changed, it has been called "disseminated neurodermatitis" or "Besnier's prurigo." Vesiculation, however, is by no means the rule, even in infancy. Among 100 cases from my files of infants under 2 years

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of age, there was exudation in only 14. The standard textbook picture of "infantile eczema" is a crusted, oozy face. As a matter of fact, not uncommonly, even in infants, the morphology more closely resembles that of disseminated neurodermatitis than that of eczema. Atopic dermatitis is not primarily, even in the infant, a disease of the epidermis; it is a disorder of the upper corium, with secondary epidermal involvement.

If one wishes to follow European nomenclature, it seems reasonable to call the condition "eczema" when it looks like eczema and "neurodermatitis" when it looks like neurodermatitis. I can see no reason, however, for calling it "Besnier's prurigo," as Nexmand, of Copenhagen, has done in his recent excellent monograph. Nor is "allergic eczema" a good term, for it does not separate this disorder from the strictly epidermal form of allergic eczema, which bears but little relation to it. For all these reasons I like the term "atopic dermatitis," because it indicates clearly a specific constitutional disease, and not a dermatological morphology.

SIGNIFICANCE OF THE URTICARIAL-TYPE SKIN TEST

Most persons with atopic dermatitis give urticarial scratch or intracutaneous skin test reactions to protein substances derived from ingested or inhaled allergens. The urticarial skin test is widely used as a diagnostic measure to determine the allergens responsible for the dermatitis. There are objections to this. Two important ones are that the test does not reproduce the lesion of the disease, which is dermatitis and not urticaria, and that withdrawal of the supposedly offending allergens by no means consistently improves the dermatitis, nor does exposure always worsen it. For these reasons, there are those who believe that the urticarial skin test is entirely without value as a diagnostic measure and, furthermore, that the allergens which give these reactions may cause asthma or hay fever, but never dermatitis. There is considerable evidence in favor of this point of view. Some additional observations which support it are as follows:

1. Patients with atopic dermatitis due to the inhalation of ragweed pollen, house dust, or other environmental allergens show urticarial skin test reactions to these allergens which are identical with the reactions shown by patients who have respiratory allergy, but not dermatitis, from the same allergens. If the wheal reaction is the determining factor in the production of dermatitis, why does one of these patients have dermatitis and the other none, when their skins react in an identical manner to the intracutaneous injection of the allergen? Furthermore, in a patient with asthma or rhinitis from an environmental allergen who is given too large a dose of the allergen by inoculation urticaria or asthma develops, but not dermatitis. The patient with atopic dermatitis due to an environmental allergen, however, with or without concomitant respiratory allergy, when given an overdose of the allergen has a severe acute flare-up of his dermatitis and new dermatitis develops in places where there was none before.

These facts make one strongly suspect that the urticarial-type skin sensitivity is not enough by itself to produce dermatitis, and that some additional immunological situation in the skin is necessary, a situation which one might call the "X-factor." It may be that the X-factor is a more superficial sensitivity, possibly of the epidermis, than that responsible for the wheal, and that for the production of the lesion of atopic dermatitis a combined deep and superficial sensitivity is necessary. If this

were so, however, it should be possible to demonstrate the superficial part of the combination by means of the patch test. This cannot often be done, and, furthermore, patch test reactions with environmental allergens, such as pollens, silk, and feathers, are obtained as often in respiratory allergy when there is no dermatitis as they are when dermatitis is present.

2. If I passively sensitize a site on my own skin with serum containing egg reagins from an eczematous infant and after a few hours eat an egg, or indeed a small amount of egg-containing food, in about half an hour an urticarial wheal will develop on the sensitized site, but never dermatitis. This reaction takes place only if the serum used is of high antibody titer and the site is, therefore, strongly sensitized; the urticarial reaction is a sudden and a violent one, and a high degree of skin sensitivity is required before it can be produced by the ingestion of a food. The dermatitic reaction, on the other hand, as it occurs naturally in infants, is a delayed reaction and can take place when there is only a moderate or a low degree of urticarial type skin sensitivity. If I sensitize my skin, however, with a serum which is not of high titer, and thereby produce urticarial sensitivity of moderate or of low degree, I can eat an egg every day with no reaction of any sort on the sensitized site, either urticaria or dermatitis; there is no cumulative reaction. The answer is, I suspect, that the X-factor has not been produced when my skin has been artificially sensitized. The whealing factor alone has been produced; infants with naturally occurring active sensitization have both the whealing factor and the X-factor.

When a small needle is introduced into the skin, the point lies in the midcorium, but by diffusion the injected liquid presumably sensitizes the vessels lying above the point of injection, as well as those adjacent to it, as the pressure of fluid when injected with a 26- or 27-gauge needle is enormous. It is possible, however, that the sensitization caused in this way is not superficial enough to produce the hypothetical X-factor. In order to test this possibility, the keratin layer of a small place on my arm was scraped off, without drawing blood, and a pledget of gauze saturated with a strong egg serum was applied and changed several times when it became dry. The next day a patch test was done with an egg-white solution and left in place for 24 hours. There was no reaction of any sort. It is evident that the sensitizing serum does not reach the small superficial vessels as well when applied from the surface, even with the keratin layer removed, as it does when injected into the corium, in spite of the fact that the actual site of the injection is well below the vessels of the papillae. Nor is it possible to sensitize the epidermis in this way. This is to be expected, in view of the fact that the epidermis contains no blood vessels and that the chief affinity of the antibody concerned is for vascular tissue.

I cannot produce atopic dermatitis on myself in any way yet tried, even though there is a good sensitization of the midcorium and upper corium. The urticarial factor is there; the X-factor is not. In order to understand the pathogenesis of atopic dermatitis, it should be produced artificially in some way on a normal subject. I have not been able to do it.

These experimental and clinical observations make a rather strong argument in favor of the thesis that the urticarial skin test is of no importance as a diagnostic measure in atopic dermatitis.

There is one solid and indubitable fact, however, which is in complete disagreement with this supposition. Anyone who has had much experience with the disease

has many times seen it alleviated by the removal of some allergen or allergens, either inhaled or ingested, which gave an urticarial skin test and has seen it recur when the allergen was ingested or inhaled again. This is beyond argument; it happens without a doubt, but by no means always. This set of reactions was affirmed experimentally by Tuft not long ago for house dust, and the studies were reported in *The Journal of Allergy.*[1] He could produce or aggravate atopic dermatitis at will in a man who gave an urticarial skin test reaction to house dust, by having him inhale a micronized dust extract, and he could cure the patient at will by keeping him in hospital environment where there was little or no dust. The same thing has been noted repeatedly in practice by many investigators for various other environmental allergens and for foods.

Here, then, are two diametrically opposed viewpoints, with strong evidence in favor of each. In order to formulate any hypothesis concerning the pathogenesis of atopic dermatitis which has likelihood of being at least partially correct, it is necessary to reconcile them.

There is a small group of physicians from various parts of the country which has met yearly in New York for the last 15 years for friendly argument and discussion on matters connected with allergy. One dermatologist, two immunologists, and eight allergists are in the group. Two years ago half a day was spent discussing the pathogenesis of atopic dermatitis, and, after considerable argument, a working hypothesis, which is a much more speculative thing than a theory, was drawn up and agreed to by all.

This hypothesis was as follows:

1. So-called protein allergens can and do excite or aggravate atopic dermatitis. These may or may not give skin test reactions of the urticarial type. This does not presuppose that the wheal reaction produces the lesions of atopic dermatitis or that it is a consistently reliable index of causation.

2. The occurrence of the wheal by itself does not produce the characteristic lesion of atopic dermatitis. In addition to it, one or more added factors, the X-factors, are necessary.

3. The wheal test reaction is sometimes of diagnostic and etiological significance, because the whealing factor and the X-factors often exist together. If the whealing factor alone is present, the urticarial-type skin test reaction is of no significance so far as atopic dermatitis is concerned.

It will be particularly noted that no mention was made of what the X-factor or factors might be; nobody knew.

SKIN TESTS WITH FOODS IN ATOPIC DERMATITIS

It is a fact that most atopic persons, with either respiratory allergy or dermatitis, give positive urticarial skin tests to a wide variety of foods. It is also a fact, particularly if the skin test is done by the intracutaneous method, which will detect a much smaller degree of skin sensitivity than the scratch test, that the majority of such reactions are of no significance so far as the symptoms under investigation are concerned.

1. Tuft, L.; Tuft, H. S., and Heck, V. M.: Atopic Dermatitis: I. An Experimental Clinical Study of the Role of Inhalant Allergens, J. Allergy **21**:181 (May) 1950.

Tuft's patient with dust dermatitis had 24 positive tests to various foods; none of these had anything to do with his dermatitis. In 1949 I reported on a series of 100 asthmatic children, with particular reference to food allergy. There were in this group 218 positive scratch tests to foods; if the intracutaneous test had been used, there would have been many more positive reactions. Of the 218 positive scratch tests, only 44, or about 20%, were of any clinical significance, and 38 of the 44 were accounted for by five foods: egg white, walnut, peanut, chocolate, and fish.

In 1950 Leibowitz, Chester, and Markow [2] reported on 70 patients with respiratory allergy. There were in this group 1,732 positive tests to foods obtained by the intracutaneous method, an average of 25 to a patient. Eighty per cent of these tests were only slightly, but definitely, positive. This is of considerable significance as will be shown later. They studied very carefully the clinical importance of 1,168 of the positive tests and found that only 4.5% were of significance. In about a third of the patients, however, it was noted that some food could produce asthma or rhinitis. Therefore, although the percentage of positive tests that had anything to do with the disease was low, the percentage of patients in whom food could produce symptoms was higher. This is important. Somewhat the same situation holds for atopic dermatitis.

What conception should be taken of positive skin test reactions to foods in atopic persons, and why is it that so many of the foods have no etiological significance?

As far as atopic dermatitis is concerned, it would seem that unless the whealing reaction is accompanied with the X-factor no dermatitis will result if the food is ingested. For respiratory allergy the situation is somewhat different, for the edema reaction taking place in the mucous membrane of the respiratory tract is equivalent to urticarial reaction in the skin. The urticarial skin or mucous membrane reaction is dependent upon two variables: the amount of antibody fixed in the tissue, and the amount of antigen which contacts it. If there is a large amount of antibody, there is a high degree of sensitization and a small amount of antigen will produce a reaction; if there is a small amount of antibody fixed in the tissue, there is a low degree of sensitization and it takes a large amount of antigen to produce a reaction. This can be readily demonstrated by sensitizing a number of skin sites with different dilutions of a reagin-containing serum, and then testing these sites with varying concentrations of antigen.

Everyone, atopic or nonatopic, normally absorbs minute amounts of antigenic food protein, and this in the atopic person very readily sets in motion the immunological mechanism which produces sensitization of skin, mucous membrane, or other tissue. There is some reason to believe that, just as in animal anaphylaxis, it takes a much smaller amount of antigen to sensitize than to shock, although this is by no means certain. Some of the sensitizations produced by the absorption of unsplit food protein may be of high degree; more frequently they are not. After tissue sensitization has taken place, if it is of high degree, the absorption of only a very small amount of antigen, such as is ordinarily absorbed, will bring about a reaction; if tissue sensitization is of low degree, the amount of antigen necessary to cause a reaction is greater than is ever absorbed, and, therefore, no reaction takes place. This rather

2. Leibowitz, H.; Chester, A., and Markow, H.: Importance of Foods in Patients as Determined by Skin Testing and Intentional Feeding, J. A. M. A. **144**:990 (Nov. 18) 1950.

simple but, it seems to me, plausible theory is based upon experimental evidence which it would take too long to discuss.

I look upon most positive skin tests to foods as normal phenomena for the atopic person; they are an indication of his constitution, and the majority of them mean nothing more than that he is an atopic person. I most emphatically do not wish to give the impression, however, that skin testing with foods is a useless procedure and never gives information of value; this is far from the truth. Used intelligently and interpreted intelligently, skin testing with foods is sometimes of great value; used without common sense, as it too often is, it is one of the most foolish things done in medicine to-day.

EGG-WHITE REACTION IN INFANTS

The egg-white reaction in infants with atopic dermatitis is of considerable interest, and, I think, possibly of some importance. Most infants with atopic dermatitis have it, often in high degree, so that it is possible to produce shock even with the small amount of egg-white protein contained in an intracutaneous testing solution. In most of these infants, ingestion of egg causes swelling of the lips and vomiting. If they absorb an appreciable amount, urticaria is likely to develop immediately, and whatever dermatitis they have is greatly aggravated several hours later. Inasmuch as hardly any of them have ever eaten egg white, the ingestion of egg white has certainly not caused their dermatitis or kept it going after it has once started. The origin of such egg sensitivity is not entirely clear. Dr. Bret Ratner has explained it on the basis of active intrauterine sensitization, and, although objections have been raised to this theory, I am inclined to think it is right. Moro, of Heidelberg, is of the opinion that egg-white sensitivity may be looked upon as the starting point of allergy in these infants; that once they are sensitized to egg other sensitivities develop more easily, and that their skins react more readily to other nonspecific stimuli. He has called this "parallergy," and it has always seemed to me that there is a good deal of sense to this conception and that egg-white sensitivity may be looked upon as the infant's initiation into the allergic fraternity.

This phenomenon is so constant and so striking in these infants, and the withdrawal of other food and environmental allergens is so often ineffective, that I have never been able to get the idea quite out of my mind that it may have a good deal to do with the production of dermatitis, even without contact with the corresponding allergen, but I certainly have no conception of how this might operate. It is an interesting fact that, while most infants with atopic dermatitis give positive skin tests to egg white, such reactions are uncommon in asthmatic infants unless they have dermatitis as well.

Whatever the relation of egg-white sensitivity to the atopic dermatitis of infants may be, a positive scratch test is of some value in differential diagnosis, because infants with eczematoid eruptions which are not atopic dermatitis do not give it.

LEINER'S DISEASE (ERYTHRODERMA DESQUAMATIVA) AND ATOPIC ERYTHRODERMA

Leiner's disease, or erythroderma desquamativa, as it is sometimes called, was until a few years ago common in Europe. It has been seen rarely in this country. It occurs as a rule in infants under 3 months of age. It is characterized by partial or complete erythroderma with scaling. The scales are usually thick and yellowish.

There is almost always an extensive seborrheic dermatitis of the scalp. The disease often begins as an intertrigo of the groins, of the axillae, or of the area around the umbilicus and extends rapidly, so that in severe cases the entire skin surface is involved. There is no vesiculation; this is a scaling eruption. There is little itching, no eosinophilia, no positive egg test, or other evidence of allergy. There may be slight general enlargement of the lymph nodes, but never of high degree. These lymph nodes do not suppurate. There are frequently a low serum protein level, with consequent edema of the legs and face, and almost always diarrhea. Either these babies recover in a few weeks, with no subsequent dermatitis, hay fever, or asthma, or they die. The mortality rate is fairly high.

Leiner's disease is generally regarded by those who have had the most experience with it as a high degree of seborrheic dermatitis. The causation is obscure. For treatment a high-protein, low-fat diet is of some value, and good results have been reported by some observers from the feeding of raw liver. Other than this there is no specific treatment.

I have seen in the last 30 years among about 4,000 patients with "eczema" perhaps 6 infants with classic Leiner's disease, corresponding in every way to the European descriptions. I have mentioned this disease because, although it is very uncommon in America, a variant of it, which I call "atopic erythroderma," is commoner and of very considerable interest. I have seen about 75 patients with this disease.

In atopic erythroderma the skin all over the body is bright red and somewhat thickened, and, as a rule, vesiculation is not prominent. Occasionally there may be but little scaling, but in most cases tremendous scaling is the most prominent feature; I keep a dustpan and whisk broom to sweep the scales off the rug after one of these babies has been in my office. The scales are exactly like those of Leiner's disease. A very marked general enlargement of lymph nodes is always present and is the most characteristic diagnostic feature. This enlargement occurs especially in the groins, axillae, and occipital regions and the nodes may reach the size of golf balls. They frequently break down and suppurate. The feet are cold and blue, and one of the first signs that the infant is improving, as he usually does in several months, is that his feet are not so blue. The itching is terrific; the baby is a picture of the utmost misery.

In contrast to those with Leiner's disease, all babies with atopic erythroderma are strongly allergic. Of 23 of these infants tested by the indirect method, 23 had egg reagins, usually of a very high titer, 19 had wheat reagins, and 10 had milk reagins. They are prone to infection, nasopharyngeal, otitic, and pulmonary. The white blood cell count is usually high, even in the absence of detectable infection. This increase of white blood cells is accounted for mostly by eosinophiles, which may make up as much as 40% of the total white blood cell count. These infants may die, but most of them gradually recover sometime during the second year. The lymph nodes become smaller, patches of white skin begin to appear, and a moderate amount of ordinary atopic dermatitis remains, or sometimes the skin may be entirely clear. Every one of them that I have been able to follow over a period of years has later had asthma or hay fever. Allergy possesses them; they are saturated with it. They are the most allergic of all persons.

This syndrome seems to be a mixture of the elements of seborrheic dermatitis, whatever they may be, and of atopic dermatitis. Instead of the usual papulovesicular eczematous reaction, the reaction is one of scaling, and in some of these infants, who are all so highly allergic, the skin manifestations are exactly those of Leiner's disease, which has nothing to do with allergy. I have seen several infants who at the second or third month presented all the characteristics of classic Leiner's disease, so that that diagnosis was made, but, as they grew older, it became evident that they belonged in the atopic group; they began to have severe itching, eosinophilia, positive egg tests, and general enlargement of the lymph nodes, went through the usual course of atopic erythhroderma for several months, and later had asthma or hay fever. I have seen, in contrast, within the last four years, two infants who looked exactly like these others did in the beginning, but they were not at all allergic, had entirely normal skins after a few weeks of treatment, and showed no subsequent allergic symptoms. There is surely some relation between atopic and seborrheic dermatitis in infancy, and mixed forms are not uncommon. Seborrheic dermatitis often precedes atopic dermatitis.

Removal of the foods to which infants with atopic erythroderma show positive skin tests or reagins does not cure them, nor does removal of environmental allergens, although some of them have reagins to feathers and house dust. They do no better in the hospital than at home. They are seriously sick infants, and the best treatment is to maintain their nutrition by proper feeding, to pay a great deal of attention to local treatment of the skin, and to try to keep them free from infection.

I have gradually come to the belief in the last few years that bacterial sensitization, usually from a focus in the nose or throat, and low-grade infection of the skin, without pustulation, are of paramount importance in perhaps the majority of these babies. The great general nodular enlargement is very suggestive; ordinary atopic dermatitis never causes it to such a degree. The fact that these lymph nodes often suppurate is important. Furthermore, furunculosis is not uncommon. Cultures of the skin usually show Staphylococcus aureus in large numbers; less frequently a Streptococcus is recovered.[3] Several times I have seen the skin of the mother's forearm become infected where the baby continually rubbed against it when she was holding him, and once a father acquired sycosis from the baby's rubbing against his face. These things happened when there was no gross infection (pustulation) on the baby. The high white blood cell count is also suggestive; the count is almost always elevated, even in the absence of pustulation.

Some of these babies have a purulent nasal discharge or infected tonsils, and in two cases an identical Streptococcus was recovered from the nose and from the skin. I have seen one infant in whom, after a purulent nasopharyngeal infection, an ordinary atopic dermatitis of no great moment changed in a few days into an atopic erythroderma which lasted many months. In many of these patients, however, no focal infection can be demonstrated.

I recently reviewed the autopsy protocols of 26 infants with severe eczema who died in the wards of the Children's Medical Center, many of whom had the symp-

3. Boisvert and Powers in 1944 emphasized the frequency of Streptococcus skin infection in eczematous infants (Boisvert, P. L., and Powers, G. F.: Eczema and Hemolytic Streptococcal Disease in Children, Yale J. Biol. & Med. **16**:595 [May] 1944.). In my material Staph. aureus is more frequently found.

tom complex I have been describing. Almost all of them died of infection, usually with Staph. aureus, but occasionally with a hemolytic Streptococcus, and these organisms were recovered not only from the lungs, middle ears, and skin, but usually from the blood as well.

One microscopic study of the skin was of particular interest:

> Clusters of bacteria on the surface were found; penetrating fissures in the epithelium and clusters of cocci in the perivascular areas were noted. There was a marked acute inflammatory cell infiltration about the small vessels of the corium.

The situation was summed up by Dr. Sydney Farber, head of the pathological department at Harvard Medical School, in a note he wrote on another of these protocols: "The cause of death appears to be a generalized infection superimposed upon an already weakened and chronically ill infant."

I look upon atopic erythroderma as a combination of seborrheic dermatitis, atopic dermatitis, and infection.

If this is true, efforts should be made to get rid of any focal infection and to keep down or eradicate whatever bacteria are growing in or upon the skin. This is surely rational treatment and should be carried out for all these patients, but is not likely to be followed by quick results. In the course of time it does benefit the patient. I have treated only one of these infants with corticotropin (ACTH); he was cured in about three days and remained so for about two weeks while he was taking the drug, but three days after its administration was stopped he was worse than he was in the beginning. Small maintenance doses did no good; he needed 40 mg. per day. DiGeorge and Nelson[4] have had the same experience with three of these infants. Inasmuch as evidence keeps accumulating that cortisone and corticotropin may lower resistance to infection and as infection is so prominent in this disorder, with further experience it may become evident that hormonal therapy is contraindicated. It is probable that a low-fat, high-protein diet is of some value, particularly for the seborrheic part of the picture and also because it is not uncommon for a low serum protein level to develop with troublesome edema, most likely due to the large loss of nitrogen from excessive scaling. Such a diet is accomplished by using a partly skimmed milk with the addition of 3 or 4 tablespoons of calcium caseinate (casec®) to the quart (45 to 60 cc. per 1,000 cc.). The rest of the diet consists of oats or rice, string beans, carrots and squash, ripe banana, prune pulp, and applesauce, a multivitamin preparation (vi-penta® drops), and ascorbic acid. These babies are in for a long siege of sickness, and it is of the utmost importance that they get an adequate diet which they can digest and upon which they will thrive. A milk-free food, such as the soy bean preparations (mull-soy® or sobee®) or a predigested protein preparation (nutramigen®), should not be used; it does them no good and may do harm by causing diarrhea. Atopic erythroderma is not due to milk sensitivity, and a milk-free diet will not cure it. It is best, however, to feed these babies no wheat or egg and to use a simple diet containing relatively few foods. More good will accrue by keeping them in a thriving state of nutrition and by a vigorous and persistent attack against skin and focal infection than by any other measures. There will be no quick cure, no matter what is done.

4. DiGeorge, A., and Nelson, W. E.: Some Observations on the Use of Adrenocorticotropic Hormone in Atopic Dermatitis in Infancy, J. Pediat. **38**:164 (Feb.) 1951.

PRACTICAL TREATMENT OF ATOPIC DERMATITIS

Although an allergist by profession, and as I wish to speak the truth, I must say that most of the time skillful local treatment does more good for infantile atopic dermatitis than anything else. However true this may be, if an attempt to get at the cause of the disease can be combined with local treatment, better results may sometimes be obtained. Etiological sensitivity to foods is common in infants and is fairly frequently detected by the skin test or by the history. Milk is of some importance, and it is here, in cases of ordinary atopic dermatitis, that the milk-free foods are sometimes of value, but at present they are being used altogether too much for every possible sort of skin eruption. Goat's milk only occasionally benefits milk-sensitive infants with atopic dermatitis, for the caseins of goat's and of cow's milk are identical immunologically and chemically, and, although the two lactalbumins are not identical, there are frequent crossed reactions. It is best not to use a soy bean food for infants under 4 months of age; these foods are too likely to give them diarrhea. For infants of this age nutramigen® is preferable. Inasmuch as the change from milk to a milk-free food is a radical one, I do not like to feed an eczamatous infant a milk-free food unless a skin test with milk has been done and is positive. It is possible to get a better idea of what the rest of the diet should be if skin tests are done, but, if a few foods which are common troublemakers are removed, the immunological indications will be rather closely met without doing skin tests. It is always well to prescribe a diet containing relatively few foods, and an infant can thrive indefinitely on a very simple diet, provided it is well balanced. The diet mentioned in connection with atopic erythroderma fulfills these requirements.

Environmental allergens, particularly wool, feathers, and house dust, are also important even in infants, and, if the dermatitis begins rather late, that is, toward the end of the first year or later and starts in the flexures of the arms and legs rather than on the face, these allergens are more likely to be a cause than are foods. I have seen atopic (contact) dermatitis due to birch and oak pollen in a child 15 months of age.

In spite of all attempts to discover specific allergens which are responsible for infantile atopic dermatitis, what one very often has to deal with is an obviously allergic baby having a positive egg test who cannot be shown to be etiologically sensitized to anything else. There is much that is obscure concerning infantile atopic dermatitis.

There is no doubt that orally administered cortisone can be of great value for certain patients in whom the dermatitis is strictly seasonal or of relatively short duration. The infant with dermatitis due to birch and oak pollen of whom I spoke was this last spring, his second season of trouble, almost entirely cured of the dermatitis while he was receiving cortisone orally during most of the pollinating season; when the medication was discontinued, there was no recurrence, inasmuch as the tree pollen season was over. My experience with cortisone given orally in maintenance doses over long periods is as yet too small to warrant any valid opinion concerning its place in the treatment of infantile atopic dermatitis in patients for whom it might be necessary to continue such medication for months or even years, rather than weeks.

I said some 15 years ago:

> To talk about infantile eczema is easy and always pleasant; to cure the patient is quite another matter, and I have seen nothing in the literature, including my own contributions, which leads me to believe that anyone really understands it, or that there is any method of treatment, dietetic or otherwise, that is consistently and entirely satisfactory.

I say the same thing today.

Until there is some method of abolishing the peculiar immunology of atopic persons, there can never be a really satisfactory way of dealing with them. When they are exposed to antigens, they begin to make a different sort of gamma globulin from that they made before, one which contains the sensitizing antibody. The extraordinary thing is that they are likely to do this for many years, whether or not they are exposed to the antigen which caused the change in the beginning. If they could be dealt with in such a way that they would revert to their previous status and make normal gamma globulin again, their troubles would be over.

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FERDINAND VON HEBRA AND THE VIENNA SCHOOL OF DERMATOLOGY

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FERDINAND VON HEBRA has rightfully been called the founder of modern dermatology. His stimulating discoveries and teachings, together with those of his successor, Kaposi, and his later followers in Vienna, laid the foundations for present-day dermatology and brought about its development as a separate, well-defined branch of medical science. It was von Hebra who established the Vienna School as the center of dermatological training and research in Europe, and indeed throughout the world, during the latter part of the 19th century.

Von Hebra was the first to apply modern research methods to dermatology, the first to cut through the maze of antiquated and conflicting theory and practice concerning diseases of the skin, and the first to create and perpetuate a genuine and widespread interest in dermatology. Von Hebra, the clinician Skoda, and the pathologist Rokitansky have been referred to as the glorious triumvirate, since they brought honor and fame to the entire Vienna School and established it as the center of all medical learning.

GENERAL HISTORY

The difficulty of von Hebra's task can hardly be overemphasized. He began his work in 1841, when dermatology as such was practically nonexistent, at a time that pathologists, who were only incidentally interested in skin diseases, were responsible for what knowledge there was of the subject.

Other branches of science had fared better. Most of the scientific inquiry of the times had been directed toward botany, zoology, anatomy, and, to some extent, general medicine. However, some work had already been done on the pathology of skin diseases. The Viennese physician Plenck, as early as 1777, had generated the first impulse for a scientific dermatology by attempting to classify and describe certain dermatological diseases. In England, Willan and his pupil Bateman had also contributed important work, collecting dermatological facts which were useful until the 1840's. In France, the Willan-Bateman traditions were augmented by the nearly classic findings of Lorry and Sauvage in the 18th century and were further developed at a later date by Alibert, Biett, Rayer, and others. Even in Germany there existed, in the 1830's, some desire to acquire dermatological knowledge, though manifested only by translations by Behrend, Riecke, and others of good French and English dermatological books. Efforts were made by the pathologist Schönlein and his pupil Fuchs to create interest among physicians in the treatment of skin

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diseases. These brief individual and meritorious attempts to develop knowledge of dermatology were allowed to wither for want of interest. No students came forth to elaborate upon the views of Plenck, Willan, Bateman, and the others and to supplement their empirical knowledge. There was no effectual communication of ideas, no adequate research based upon critical observations, no concerted effort to improve and to modify existing knowledge of skin diseases.

Ever since the Dark Ages skin diseases had been identified mainly with leprosy and venereal diseases and had been treated as contagious. Both patients and researchers occupied in this field had been held in low esteem. This naturally tended to discourage serious scientific effort. Concomitant with this popular conception, pathology in general and dermatological pathology specifically were strongly influenced by the humoral theory. This prevailing conception taught that there were four basic fluids of the body, and that imbalance of one or more of these was responsible for disease. The idea that morbid juices caused diseases permeated and dominated all scientific thinking. It followed that local skin therapy was rejected for fear of damaging the inner organs.

As late as 1840, one year before von Hebra began to study skin diseases, medical men in Vienna were contending that changes in the skin were the result of internal organisms attempting to reach light and air. It was considered dangerous to disturb these manifestations, representative of inner secretions. All that was done was to classify the different skin manifestations according to a botanical system. The skin changes were symbolized as germination, growth, and withering of the blossoms. Sedimentation of the blood, milk, bile, and urine was believed to be involved.

Despite the fact that the pathologist Peter Frank distinguished between the acute exanthems and the chronic efflorescences, the field of dermatology in general lay fallow, awaiting the great scientific stimulus which von Hebra was to give it.

HISTORY OF THE VIENNA SCHOOL

Through the late 1830's the Vienna School, which included the University of Vienna and the closely associated Vienna General Hospital, reflected in its teachings the prevailing humoral theory and lack of integrated scientific achievement.

In the Vienna General Hospital, all skin-disease patients were placed together, without regard for the nature or severity of their conditions; syphilitics and mental patients were also included in this milieu. Since there was no separate clinic, the patients were under the supervision of the chest-disease department, headed by Skoda. An annex, called the "Scabies Station," housed these patients. All chronic skin diseases at that time were classified as scabies, regardless of symptoms. Because there was no true understanding of the character of these diseases, no adequate forms of treatment had been devised.

From about 1840 on, however, conditions in the Vienna School began to improve rapidly. Rokitansky, who taught at Vienna, published his important textbook on pathological anatomy, and his new doctrines finally came to dominate the Vienna School. His power of precise morphological observation and his ability to arrange characteristic features in groups and to combine them into living pictures caused his fame to spread. A new attitude of critical observation was introduced.

Skoda, pathologist and clinician, worked in close cooperation with Rokitansky and added another vital ingredient to the new school of scientific thought, that of the power of critical evaluation of data acquired by physical methods. Skoda asked

for undisturbed observation of the effects of medication and was reluctant to proceed without proved facts, while Rokitansky was prone to arrange brilliant observations in a somewhat haphazard manner. It was von Hebra who was later to combine the best virtues of both men. He utilized his great powers of observation to collect copious and pertinent data and his sharp intellect, well controlled by common sense, to reach significant verifiable conclusions. While Rokitansky emphasized the philosophical and dealt with abstract ideas, von Hebra always dealt with practicalities and sought a firm foundation in fact.

VON HEBRA'S EARLY LIFE

Ferdinand Ritter von Hebra was born at Brunn in Moravia, on Sept. 7, 1816, the son of a quartermaster in the Austrian Army. The frequent changes of domicile attendant on army garrison life prompted the boy to an early separation from his family. He attended high school at the Judenburg monastery in Styria and then spent two years in required philosophical studies at the University of Graz in Styria. After his medical course at the University of Vienna, which he completed in 1841, he obtained an assistantship in the department of medical jurisprudence at the University. Here von Hebra put his powers of acute observation and description to good use as he performed postmortem examinations under the guidance of Rokitansky. This period of his life enabled him to develop his knowledge of pathology.

With Skoda's help, young von Hebra was appointed as his assistant, in November, 1841. Skoda at the time was head of the department of chest diseases at the Vienna General Hospital. It was von Hebra's first contact with skin-disease patients, and he found himself much interested in their plight. Skoda, noting his pupil's interest, then asked him to specialize in this subject, to read and to devote all his time to it. Skoda realized that this badly neglected field was fertile ground for a man who demonstrated a highly developed ability for critical observation and deduction. Von Hebra followed the suggestion and thus began the career which was to bring him lasting recognition and security and, above all, was to create and develop the science of dermatology. Considering the low opinion in which the field was held and the conditions with which von Hebra was confronted in the skin-disease ward, this was indeed a heroic decision.

Skoda acted quickly to aid his enterprising pupil, appointing him head of the "Scabies Station." Though famous, Skoda himself was, at that time, only the chief of the clinic. By voluntarily relinquishing to von Hebra a part of his authority, Skoda demonstrated his true consideration and kindness. He also arranged to place all available tools at the young intern's disposal, giving him his first books on dermatology and counseling him in methods of study. He urged von Hebra to apply the principles developed by Rokitansky and used by Skoda himself with such success: observing the conditions of the skin minutely, sampling, and comparing and evaluating data. Above all, Skoda gave von Hebra free rein to carry on his studies and encouraged and guided him in his work.

In the following months the young assistant did a tremendous amount of reading, made many observations, and almost immediately began to conduct stimulating lectures to select groups of physicians, many of them older, well-known men. His lectures were at first directed toward the explanation and presentation of the delicate system of classification of skin diseases devised by the French physician Alibert;

this system he compared with the findings of Willan and Bateman, whom he much respected for their clear and concise methods of data presentation. In order to legalize his lectures, von Hebra asked the Government of the Province of Lower Austria to grant him the title of academic lecturer (or assistant professor). He explained there was an urgent necessity for physicians and medical students to have a firm foundation in the diagnosis and treatment of skin diseases. In spite of opposition, the appointment was finally granted, in October, 1844, on a nonsalary basis, more than two years after the lectures began. Thus, dermatology was recognized as a teaching subject for the first time.

During the formative period of his life from 1841 through 1845, von Hebra occupied himself with much hard work. He continued his lectures and scanned all relevant literature on skin diseases. He also supervised the skin-disease section, experimented with various therapies, and investigated the etiology and pathology of a number of skin diseases.

Von Hebra's lectures gradually increased in merit. His method of presentation was always excellent, straightforward, witty, and strongly practical. It seems incredible that in 1842 he still believed that the interior organs were sick and that lesions of scabies were forced from the inner organs into the skin. Gradually, however, he began to be critical of this theory about "the itch." He experimented in transferring the Sarcoptes mite to himself and other persons again and again and observed the primary and secondary changes in the skin.

More and more, personal clinical observations, achieved through the methods suggested by Skoda and Rokitansky, were making deep inroads on the writings of the earlier proponents of the humoral theory. By 1843, as an assistant, von Hebra had acquired a tremendous amount of useful data selected from his own cases and from the available literature. He grew dissatisfied with the humoral explanations of disease. Indeed, Willan gave no pathological explanation at all for the observed skin phenomena, although his descriptions were excellent. Therefore, von Hebra gradually developed cogent explanations of his own, which were a synthesis of the methods of Rokitansky, Kolletschka, and Skoda applied in combination with his own observations to his own field of dermatology. The new dermatology he was evolving can correctly be called the daughter of the new pathology.

By 1844 the results of von Hebra's studies on scabies appeared in the form of a paper and created a sensation. The presence of the Sarcoptes mite in scabies had been known for a long time but the essential relationship between the mite and the skin changes was elucidated for the first time, proving conclusively the external causation of the disease. Von Hebra based his theories entirely on facts drawn from personal observations. Even the great anatomist, Hyrtl, congratulated the young assistant on his exact methods of investigation.

Von Hebra concluded as follows:

1. Everyone acquires scabies if the Sarcoptes mite settles on his skin.

2. The condition is eradicated when the mite and its eggs are destroyed.

3. Mechanical, chemical, and caloric irritations can produce such varied manifestations of the disease as hyperemia, exudations, nodules, bullae, pustules, and eczema by irritating sensitive capillary vessels and other skin tissue.

4. The skin irritation can be transferred to a distant site on the skin by nerve reflexes.

Von Hebra's work on scabies led him further to investigate eczema. He noted these facts:

1. Eczema develops if proper chemical or mechanical irritation attacks the skin.

2. New eczematous eruptions are due partly to mechanical irritation and partly to a disturbance of innervation.

In his tests he showed that artificial eczema caused by the application of arnica to the pubic region can manifest itself in eruptions on the face.

Von Hebra's description and explanation of eczema, together with his paper on scabies, were great achievements and formed the basis for his doctrines. Their immediate recognition as outstanding works encouraged him to continue and to apply Skoda's methods to the study of other skin diseases. In each investigation he attempted to state the cause of the disease as either external or internal and to characterize its influence on the health and life of the patient. He related the observed physiological development of each disease to the macroanatomical and microanatomical changes.

As the role of skin diseases in pathology became clearer to him, he was able more easily to place symptoms into categories, to discuss complexes, and to differentiate among various complexes. New diseases were described with great accuracy, and a method of systematizing diseases on the basis of their clinical phenomena emerged. Though it was originally Rokitansky's idea to establish a morphological examination as the basis of an anatomical diagnosis, it was von Hebra who first successfully applied this system to dermatology.

During this period he also began seriously to test the influence of various remedies, for it was his great aim to bring to his skin-disease patients as effective therapies as had been achieved in other fields of medicine. For the first time, agents were administered topically; no longer was there any fear about their application, since he had disproved the humoral doctrines. Agents were also given internally. Von Hebra emerged not only as a diagnostician but also as a therapist.

HISTORY OF MIDDLE AND LATER PERIODS

It was in 1845 that von Hebra's ward was first separated from Skoda's department of chest diseases. This date is commemorated as the birthdate of dermatology as a separate medical science. By this date von Hebra's name was well known. In his lectures his new ideas were subject to the severest cross examination, but he met all questions with poise and explained all his findings accurately and with irrefutable logic. His audiences gradually became convinced of the merit of his theories. We find that in the period 1845 to 1848 von Hebra established himself as the foremost authority on dermatology in Europe.

In 1845 he published his "Attempt to Classify Skin Diseases on the Basis of Pathological Anatomy." This was a great work, not essentially anatomical in nature, but rather in its main phases based on the interrelationship of certain clinical phenomena with nutritional and textural changes. Von Hebra placed skin diseases into the following 12 categories:

1. The hyperemias
2. The anemias
3. Anomalies of secretion
4. Exudations
5. Hemorrhages
6. Hypertrophies
7. Atrophies
8. Benign new growths
9. Malignant new growths
10. Ulcers
11. Neuroses
12. Parasitic dermatoses

The great advantage with this system was that the skin diseases were represented in a manner similar to that of diseases of other organs, a method which served to emphasize the correct place of skin diseases in the over-all picture of pathology.

Von Hebra's success during the years 1845 through 1848 culminated with his appointment as "primarius" or chief of staff of the Vienna General Hospital in 1848 and his being named associate professor the following year.

An era in von Hebra's life in which he was to be heralded as an outstanding clinician, teacher, practicing physician, and researcher began. His appointments afforded him the financial security necessary to display his eminent talents and more fully to enjoy his pleasant home life with his wife and son. It was, however, years later, 1869 to be exact, before he attained the rank of full professor. He was the first person in the Vienna School ever to hold a permanent professorship. He received many honors, including being knighted by the Austrian government, and he made many trips to Paris and the famed Hospital St. Louis and to the London hospitals between 1852 and 1875.

His research continued. There is scarcely any form of skin disease which he did not touch on and describe as best he could. Because of the wealth of skin-disease patients whom he could observe and treat at the hospital and in his private practice, he was able to make critical commentaries based on personal observations of lichen scrofulosus, lichen planus, impetigo herpetiformis, prurigo, rhinoscleroma, and many other diseases. His motto was, "Never abandon a case as hopeless, but continue to study it on the basis of knowledge of its pathology and etiology until you find some way to help."

His methods for the treatment of eczema are classic. Although most of his therapy involved topical treatment of skin diseases, he also spent time in determining the validity of many internal remedies. He achieved success in healing lichen planus with arsenic, despite warnings from others that the method was too dangerous.

Von Hebra clearly demonstrated that he realized a basic relationship between the inner organs and the skin in such disorders as eczema, pemphigus, forms of pruritus, and chronic urticaria. He once stated that "the skin is an integral part of the whole organism and subject to the same metabolic processes as other organs." He published 32 articles on vaccination, leprosy, scabies, eczema, scabies norwegica, and other subjects.

His "Atlas of Skin Diseases," illustrated by Elfinger and Heitzmann, was prepared for use as a teaching and research tool. It took 20 years to finish and contains pictures and descriptions not only of the major diseases but also of a number of rare skin diseases.

His "Textbook of Skin Diseases" more generally outlined his theories regarding the pathology of the skin and was considered a classic compendium of knowledge on the subject. It appeared in two volumes, only the first of which was actually written by von Hebra. In this book he exactly detailed his mode of morphological observation and analysis of skin diseases, which serves as the basis of dermatological research today.

Though von Hebra realized the value of expressing his ideas through publications, his first love was lecturing, and it was on the lecture platform that his theories were first expressed. Indeed, it was his twin talent for research and teaching which eventually succeeded in firmly establishing dermatology as a separate science. He

established a teaching tradition and developed new methods for more effective presentation of his material. Since von Hebra considered every problem from a practical standpoint, he believed that his lectures should be supplemented as fully as possible with concrete living examples; his "Atlas" helped students visualize the precise clinical picture of certain diseases which were not readily available for demonstration. Theoretical discussions were avoided in his lectures; he stuck strictly to facts, never failing to disclose all or at least the best of what he knew on a particular point. He was most anxious for all his students to understand clearly and fully all the subject material he presented. Though von Hebra's style was rather blunt and sometimes clumsy, he brightened the lecture hours with witty remarks and a general feeling of frankness, earnestness, and good humor. Fact was everything to him; observation of the human body was his source of knowledge and the main focus in his lectures.

In later years von Hebra was not free to spend as much time lecturing or carrying on research; relaxation was required. Since early childhood he had suffered from bronchiectasis, and the chronic catarrhs were often accompanied with fever. Dilatation of the heart and congestion of the liver and kidneys gradually complicated his condition. Instead of retiring to his farm in the green Styrian mountains to enjoy rest and pursue his love of nature, he spent the last weeks of his life tortured by asthma and dropsy until relieved by a gentle death on Aug. 15, 1880. His hearse was followed by his many friends and by thousands of Viennese who mourned the passing of their great benefactor. He was buried in Hernals, Austria, in a plot next to that of his lifelong friend, the great Rokitansky.

INFLUENCE OF VON HEBRA ON THE VIENNA SCHOOL

Von Hebra's passing found the Vienna School at its zenith. Qualified students, on returning from Paris and other medical centers on the continent, had made it a practice to complete their education in dermatology at Vienna, where they had attended the lectures of von Hebra; they well knew he could fill in their educational gaps on skin diseases which had not been touched upon elsewhere and offer cogent explanations of obscure points. Since his conceptions were realistic, descriptive, and phrased in simple vernacular, pertinent knowledge was easily acquired.

The fortunate proximity of the Vienna University to the General Hospital and its clinics offered an ideal combination. Here the best in teaching was combined with a wealth of easily accessible clinical material. Von Hebra's organization of his lecture material ideally suited this type of teaching, and so students gradually left Paris and chose Vienna. Vienna's influence, especially in the field of dermatology, was strongly felt in the second half of the 19th century, as reflected in books published in Germany, England, and America. The classic works of Fox in England, Duhring in America, Koebner in Breslau, Pick in Prague, and Behrend in Berlin were patterned after the teachings of the Vienna School. Nowhere else was learning on such a highly integrated plane.

Von Hebra well understood that to insure the Vienna School's continued supremacy in dermatology and continued progress in dermatological research there should be a well-integrated system devoted to the perpetuation and enlargement of his theories and ideals. In his lectures he emphasized to his students the qualities of diligence, patience, serious consideration of data, and an honest and real approach to research. He always encouraged his assistants in any way he could and allowed

them free rein to carry on their work. By degrees, he developed and personally trained a large number of outstanding disciples, who helped him with many of his discoveries; among them were Koebner, Auspitz, Neumann, Pick, Simon, the great Kaposi, and his own son, Hans, who for many years also taught dermatology at Vienna and who was renowned in his own right. He approved of suggestions which entailed the use of botany, chemistry, and histology, since it was always his aim and hope that these more mature sciences would advance the causes of dermatology. Hence, the mycotic and histologic work of his students was always appreciated. He not only taught his assistants dermatology as he knew it but educated them by his own example in the virile virtues of independence, loyalty to duty, and the courage to accept responsibility. He was a hard taskmaster, expecting a serious approach by the student. But his efforts bore fruits, his students carrying on in his spirit not only at Vienna but throughout other parts of Europe and in America; they enlarged upon his theories and discoveries, thereby assuring that the excellent dermatological methods and traditions established by von Hebra would not perish as did the efforts of Plenck, Willan, and Bateman.

VON HEBRA'S SUCCESSORS

Von Hebra's careful training was liberally rewarded when Moritz Kaposi succeeded him as head of the dermatology department at the University of Vienna. Kaposi had been von Hebra's most promising assistant. Born at Kaposvar, Hungary, in October, 1837, Kaposi studied medicine at Vienna from 1855 to 1861, when he received his degree of Doctor of Medicine. From 1866 to 1869 he assisted von Hebra in the dermatology clinic at Vienna and in 1867 followed in von Hebra's footseps by becoming an unpaid lecturer at the University. Later, in 1875, Kaposi became an associate professor and in October, 1881, was appointed head of the dermatological clinic of the University. It was 14 years later that Kaposi was promoted to the rank of full professor.

Although not a pioneer in the same degree as von Hebra, he continued to build up what von Hebra began and thus has been considered as a co-founder of modern dermatology. Kaposi was a man of action and was gifted with a brilliant mind. As a result of his wide knowledge and his precision as a diagnostician, clinician, and therapist, he gained recognition. He was noted for his decisive positions on all questions, and contemporaries always were anxious to hear his views. He became internationally respected when the "Handbook of Dermatology," which he and von Hebra wrote together, was published. Kaposi had the advantage of being taught by the foremost masters of his time, von Hebra, Skoda, Schuh, and Rokitansky. He was naturally attracted to clinical observations explained by anatomical findings, and his keen intellect approached every problem with an unbiased attitude. Like von Hebra, he was able to separate the essential from the nonessential and to compile composite facts into a precise clinical picture. He characterized and described many skin diseases, besides the well-recognized multiple idiopathic pigmented sarcoma, and improved existing knowledge of herpes zoster, sarcoid, lichen planus, and other dermatoses.

Kaposi was quick to grasp new discoveries and read all articles in his field, as well as much literature in other fields of medical science. So extensive was his knowledge that he was capable of giving a cogent answer to problems in many fields

of medicine. Kaposi had a tremendous capacity for work and wrote more than 100 papers, covering almost everything in the field of dermatology. His book called "Lectures on Skin Diseases" has been accorded lasting recognition.

Kaposi was above all a master therapist. It was he who first discovered the use of betanaphthol. He was also an excellent teacher and orator, with a sparkling temperament. His home and professional lives were blessed with happiness, and he had a definite ability to make friends. Despite his last painful illness, he died a peaceful death in 1902, having successfully furthered the reputation of the Vienna School and his own and von Hebra's teachings.

After Kaposi's death, the Vienna School, which by now was strongly influencing the course of American dermatology, was divided into two groups. Neumann represented one group and Riehl the other. Finger was Neumann's successor, followed by Kyrle and Kren. Many other notables, such as Matzenauer, von Zumbusch, Kreibich, and Arning, helped to establish the teachings of the Vienna School in other European centers. Ehrmann also studied under Finger, and other Vienna men who developed centers are Rausch, Oppenheim, Leiner, Simon, Neisser, and Jadassohn. Riehl's successor is our friend and teacher, Prof. Leopold Arzt, who now ably heads the dermatological department of Vienna General Hospital, another whose initial intensive training was in general pathology.

PRESENT-DAY DERMATOLOGY

We have seen that modern dermatology was given its first impetus, its first definition, and its basic set of rules through the work of von Hebra and his followers. The influence and teachings of the Vienna School of dermatology spread throughout Europe and eventually to America, bringing with it a new scientific code, a driving force, and a new established tradition.

The rise of America as the center of dermatological practice and investigation is well known. Today, the United States, with its fine schools and research foundations, sets the standards in our field. Even before the second World War, the shift of leadership in dermatology to the United States was apparent. Because of much devastation and poverty and the consequent destruction of many fine European institutions, this shift has been accelerated, until today we represent the focal point of much of the outstanding dermatological training and investigation.

In the United States there is no single group of dermatologists who follow the system of organization and dissemination of knowledge that was so necessary for the Vienna School in order for it to maintain its supremacy and to foster the field. There is no consistent passing on of painstakingly acquired specific and particular knowledge from master to student-successor in America, and, indeed, there may be no great need for such a system. Obviously, much more is known by all dermatologists today; dermatological discoveries are much more easily communicated, both through readily available dermatological publications and through a network of local, state, and national medical societies. It is apparent that American dermatologists will continue materially to contribute to progress in our field.

In summation, let us not forget that but for the tremendous strides the Vienna School of dermatology accomplished and fostered, but for the driving force of von Hebra, Kaposi, and their followers, modern dermatology might not be the highly specialized branch of medical knowledge it is today. Von Hebra earned and was

accorded his due contemporary recognition, but we of today should not lose sight of the debt we owe to von Hebra and to those who trod the path which he so painstakingly hewed for them.

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BIBLIOGRAPHY

Arzt, L.: Wien. klin. Wchnschr. **61**:863-867, 1949.

——Arch. Dermat. u. Syph. **191**:19-26, 1949.

Auspitz, H.: Vrtljschr. Dermat. u. Syph. **7**:i-xiv, 1880.

Kaposi, M.: Wien. med. Wchnschr. **31**:1207-1215, 1881.

Nobl, G., in Congressus dermatologorum internationalis, Ninth Congress, edited by L. Nékám, Leipzig, J. A. Barth, 1936, Vol. IV, p. 245.

Rille, J. H., in Congressus dermatologorum internationalis, Ninth Congress, edited by L. Nékám, Leipzig, J. A. Barth, 1936, Vol. IV, p. 299.

Spiegler, E.: Arch. Dermat. u. Syph. **60**:i-x, 1902.

Spitzer, E.: A. M. A. Arch. Dermat. & Syph. **64**:282-283, 1951.

Ullmann, K., in Congressus dermatologorum internationalis, Ninth Congress, edited by L. Nékám, Leipzig, J. A. Barth, 1936, Vol. IV, p. 367.

PARAPHENYLENEDIAMINE HAIR DYES

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HAIR DYES have been used since ancient times. There is evidence that the ancient Egyptians, Greeks, and Romans used them.

The hair dyes used by the ancients were vegetable in origin. Nutgalls, saffron, thapsia,[1] henna, indigo, camomile, sage tea, and many others were used for hair coloring. Dermatitis or systemic poisoning from hair dyes is not known to have occurred among the ancients; nevertheless, the ancient physicians were prejudiced against their use. This prejudice has persisted among physicians to the present.

Metallic salts were also used as hair dyes as early as Galen's time. Lead salts were used for hair dyeing by the ancient Chinese. Occasional cases of metal poisoning were attributed to them, but neither the disapproval of physicians nor the hazard of poisoning from improper use of the dyes deterred people from employing them. Metallic salts alone or in combination with vegetable dyes in solution or pastes (rastiks[2]) have been and are still occasionally used as hair dyes.

In 1883, paraphenylenediamine, $C_6H_4(NH_2)_2$, a crystalline, colorless compound, was introduced as a hair dye, and, despite all the adverse reports of its allergenic and allegedly poisonous effects, it has become the most widely used hair coloring. Its popularity is due to the fact that it gives the most natural appearance and is the longest lasting. Paraphenylenediamine mixtures can be made to produce colors on the hair varying from canary-yellow to jet-black.

About 95% of all professional hair dyeing or tinting is now done with paraphenylenediamine dyes, and the remaining 5%, with natural products and so-called compound hennas. Many of the compound hennas contain small amounts of paraphenylenediamine in addition to natural coloring matter and metallic salts. Among other uses of paraphenylenediamine are fur dyeing, manufacture of azo dyes, rubber vulcanization, and photographic developing.

The metallic dyes are not used in beauty shops, although they are used in some barber shops, and the so-called progressive dyes for home use usually consist of a lead salt and sulfur. The paraphenylenediamine dyes are rapidly replacing other types for home use. The home-use dyes are marketed under various names, such as hair rinse, shampoo tint, color shampoo, and hair coloring. Those containing paraphenylenediamine dyes may be recognized by (1) the "caution" notice on the

1. Thapsia, a plant from the island of Thapsos, belongs to the family Ammiaceae. There is a wild carrot, Thapsia garganica, which contains an irritating resin.

2. Rastik is a paste hair dye originally made by mixing powdered nutgalls or powdered dried walnut husks with oil, but now made from a mixture of pyrogallol, a metallic salt, and oil.

carton and labels, (2) the preliminary patch-test directions in the prescribed directions for use, and (3) the separate packaging of the two units, the contents of which must be mixed together before use.

Several authors have reported dermatitis, blindness, and systemic poisoning from paraphenylenediamine dyes. Most of the cases were reported between 1930 and 1937; the peak in the number of cases reported was in 1934.[3] Patch tests performed by various dermatologists showed that 3 to 6% of the population was sensitive to paraphenylenediamine, and laws were made to regulate its use.

Despite the widely publicized risks entailed in the use of paraphenylenediamine dyes, since their introduction they have been in continuous use both in beauty parlors and at home, and yet since 1937 the cases of dermatitis or alleged systemic poisoning attributed to them have become rare indeed. Thus, the actual use of the paraphenylenediamine dyes has not borne out the dire predictions of early writers.

The patch tests performed by some dermatologists in the early 1930's were done with high concentrations of paraphenylenediamine; the patches were covered and closed and were even of paraphenylenediamine sealed on the skin with collodion. The oxidized paraphenylenediamine, which is the actual dye, was not the material used for patch testing. It is agreed that the intermediate transitory oxidation product quinonediimine [4] is the actual allergenic agent. The completely oxidized paraphenylenediamine is acknowledged to be inert and insoluble.

If patch tests are performed by applying paraphenylenediamine on the skin as mentioned above, the oxidation of it slowly takes place on the skin, and, if the patch is covered, oxidation is slower still; thus, the quinonediimine is slowly and continuously being formed on the skin and remains there a long time before further oxidation into the harmless Bandrowski base occurs. If the paraphenylenediamine is sealed on the skin, as with collodion or adhesive plaster, so that air does not get to it, the quinonediimine may not form until the patch is unsealed, and this may account for what has been interpreted as a delayed reaction.

Other dermatologists performed covered patch tests with the mixture of paraphenylenediamine, ammonia, and hydrogen peroxide. Such mixtures containing 3 to 8% ammonia, if sealed on the skin, may well have caused primary irritation. Rostenberg and Sulzberger [5] state that the proper concentration for patch testing with ammonia should be no higher than 1 to 2%. The covered patch test does not permit the volatilization of the ammonia from the solution as happens in the actual dyeing of the hair.

The high incidence of positive reactions to patch tests previous to 1935 was also influenced by the use of impure paraphenylenediamine containing residual amounts of irritating paranitraniline, from which it was then exclusively made. Now it is also produced from the comparatively innocuous paradichlorobenzol, and pure paraphenylenediamine is used in hair colorings.

3. Schwartz, L., and Peck, S. M.: Cosmetics and Dermatitis, New York, Paul B. Hoeber, Inc., 1946, pp. 94-95.

4. Quinonediimine, $NH:C_6H_4:NH$, is the first step in the oxidation of paraphenylenediamine. Quinonediimine has a sharp penetrating odor and produces local irritation wherever it contacts skin or mucous membrane. It is unstable and decomposes or combines with itself in a short time to form Bandrowski's base, a more stable compound. Oxidation proceeds beyond this until the final oxidation product is insoluble and inert.

5. Rostenberg, A., Jr., and Sulzberger, M. B.: List of Substances for Patch-Testing, and Concentrations to Be Employed, J. Invest. Dermat. **2**:93-117 (June) 1939.

In actual dyeing of the hair two solutions, separately bottled, are used. The one bottle contains the solution of paraphenylenediamine, ammonia, and other ingredients, and the other contains the oxidizing agent, usually hydrogen peroxide. The contents of the two bottles are poured into a vessel, mixed, and allowed to stand for five minutes before being applied to the hair. The free ammonia content of the final dyeing mixture should not exceed 1.5%. This permits the oxidation of the paraphenylenediamine to go quickly beyond the quinonediimine stage. The longer the mixture stands, the less is its potential for irritation. Moreover, after the hair is dyed, a matter of less than one hour, all excess dye, ammonia, and hydrogen peroxide are washed off the hair with a shampoo.

It is evident from this that such covered patch testing as described above does not represent actual usage and that the results of such patch testing will not and did not accurately predict what would occur from actual usage of the paraphenylenediamine dyes. Such patch testing is questionable even as a diagnostic procedure for patients suspected of suffering from hair-dye dermatitis. It is somewhat similar to performing separate patch tests with sodium hydroxide and with hydrochloric acid in an attempt to predict the irritant properties of sodium chloride (salt), the end-product of the chemical combination.

A conservative estimate places the number of applications of paraphenylenediamine hair colorings now annually consumed in the United States alone at 55,000,000, with their consumption constantly increasing. A survey among their producers in 1930, when preliminary patch testing was more or less a novelty, revealed one reported case of alleged dermatitis to 10,000 to 20,000 packages sold. A recent study places the number of cases of alleged skin irritation in the ratio of one case to 40,000 to 60,000 packages distributed. This reported drop in incidence is undoubtedly the result of the increased use of the preliminary patch test, which manufacturers are now required by law to prescribe as an integral part of the instructions for use and which cosmetologists are required to perform by local laws in many jurisdictions.

In suits for damages against manufacturers of paraphenylenediamine hair dyes, there have been no recoveries since preliminary patch testing became an important part of the directions for use. Recoveries have been obtained against beauty-shop owners when it was established that the alleged injuries resulted from the negligence of the beautician in failing to make the preliminary patch test which would have disclosed the presence of a hypersensitivity to the hair coloring, and thus would have avoided the resulting skin involvement. We know of no instance in which a claim of systemic effect was substantiated. It might be pointed out that, while preliminary patch testing is required by all directions for the use of these products, such testing is not yet the universal practice it ought to be.

Considering these figures, it becomes evident that the risk of an allergic dermatitis is remote, especially if the proper preliminary patch test is employed. There are four main factors to which this great diminution in dermatitis from the paraphenylenediamine dyes can be attributed:

1. The law requires that patch tests be performed before each application of the dyes.

The patch test should be performed as follows: Five drops of the solution from bottle 1 should be mixed in a small glass with the proper proportionate amount from bottle 2 and the mixture allowed to stand for five minutes. The site to be used

should be washed with soap and water and dried. Then, with a cotton applicator, the mixture should be painted on the skin at the bend of the elbow or behind the ear, the application covering an area not less than the size of a 25-cent piece. It should be allowed to dry and to remain on the skin uncovered for 24 hours. If at the end of this time there is no itching or sign of irritation at the site of the application, the dye can be safely used on the hair. This test should be repeated each time the dye is used, even for retouching the hair. If there is any sign of irritation at the site of application, such as redness, swelling, papules, or vesicles, the dye should not be used.

This patch test, if properly performed, will weed out the possible dermatitis cases. It will also prevent those persons for whom the test is positive from using the dyes, even though actual usage of them in these circumstances by some has caused no harm.

2. There has been great improvement in the manufacture of the dyes.

Manufacturers of hair dyes now employ staffs of chemists especially experienced in hair and fur dyeing who are continually improving the formulas. The improvements consist in accurately preparing the concentration of the paraphenylenediamine solution; in supplying a sufficient amount of oxidizing agent to quickly and completely oxidize the paraphenylenediamine; in providing a final dyeing solution containing no more free ammonia than is actually necessary, a concentration below the limit of 1.5%; in adding a wetting agent to aid in wetting and dyeing the hair, and in testing every finished batch of hair coloring to insure correct fabrication.

3. Prophetic patch tests and actual usage tests are performed before marketing when new chemicals are added to the formula or when the formula is changed by increases in the potentially irritating chemicals.

4. The availability and use of pure ingredients, especially purified paraphenylenediamine, have increased.

Recently a hair dye for home use was submitted to us for a dermatological study before being placed on the market. Bearing in mind the fallacies of some previous methods, the following procedure was employed for the first series of prophetic patch tests with six representative shades of this paraphenylenediamine dye on 200 subjects.

We first mixed the contents of the two bottles of the home-use hair dye as required by the directions for use, allowing the mixture to stand for five minutes before painting it on the cleansed skin. The site chosen was the thin skin of the inner fold of the elbow. The site was first washed with soap and water and dried. The mixture of the dye was then painted on with a cotton applicator over an area not smaller than that of a silver half-dollar (later the area was increased to 4 sq. in. [25.8 sq. cm.]) and allowed to dry. The subjects were instructed not to wash the site of the patch.

The dye mixture was discarded after standing 20 minutes, and a fresh mixture was made.

The procedure was repeated with the same subjects on the same site for three successive days. Twenty-four hours after the third application the subjects were seen again and examined for reactions and then were told to wash off the dye. To do this required several days, as the skin was deeply dyed, especially where the darker shades were used.

Ten days after the last reading, the contents of the two bottles were again mixed and applied as described before on the same sites of the same subjects. Twenty-four hours later the subjects were examined for reactions and then told to report if any late reactions developed.

A paraphenylenediamine hair dye long used in beauty parlors was employed as a control patch. There were no reactions from any of the patches on any of the subjects.

This method of patch testing more nearly approximated actual usage than did the previous methods using paraphenylenediamine alone, whether covered, uncovered, or sealed on the skin. Covered patch tests with mixtures of the contents of the two bottles in which the alkaline ammonia is prevented from volatizing from the skin can well cause primary irritation.

It is admitted that, in order to be safe, prophetic patch testing should be severer than actual usage. However, the test should not be so severe as to lose similarity to actual usage. The above method is severer than actual usage for the following reasons:

1. The dye is applied directly to tender skin, whereas in actual usage most of the dye is applied to the hair and only a small part of it touches the scalp.

2. The dye is applied to the cleansed skin in patch testing, while in actual use the natural protective oils and fats are not first removed from the scalp.

3. The dye in actual usage is on the hair and incidentally on the scalp for less than an hour and is then shampooed away, whereas in our patch test it is not washed off until after 72 hours.

In actual usage the dye is applied once in six weeks, whereas in the test it was applied to the same site for 3 successive days and 10 days later was reapplied.

The patch tests were performed at various times on 1,000 subjects with 14 mixtures of different shades of the dyes, varying from canary-yellow to jet-black. These dyes contained in the tinting mixture a maximum of 1.25% paraphenylenediamine and a maximum of 1.5% free ammonia as NH_3. Altogether, more than 5,000 patches were applied to the skin of the 1,000 subjects (without eliciting any reactions). In addition, uncovered patch tests were performed by two other dermatologists on 234 women with the dyes that were to be used on their hair, and there were no reactions. In all, therefore, we have records of open patch tests as described above on 1,234 subjects without a reaction.

New batches of these dyes are being constantly tested by actual use on volunteers in laboratories. We have examined more than 600 of the 1,200 subjects who have had their hair dyed with the home hair coloring without finding any serious cases of dermatitis. We have found however, that some of them showed small isolated excoriations on the scalp a day or so after using the dye.

Close questioning revealed that at times some of these excoriations were present before use of the dye, and several women admitted that scratching with the nails or strenuous combing and brushing were the cause. The excoriations healed within one week, and there were no cases in which the excoriations recurred with repeated use of the dye.

Six women among the more than 600 examined stated they had skin inflammation subsequent to using the dye. The complaints were as follows:

1. Swelling of the face occurred, which was no longer present at the time of the examination one week later.

2. A small area of lichenified eczema was observed on the back of the neck.

3. Mild seborrheic dermatitis on face was noted.

4. One woman stated that she had an irritation of the scalp and stinging of the eyes on application of the dye to the hair, symptoms which disappeared the next day. There was no sign of any dermatitis at the time of the examination.

5. One woman reported a reaction at the site of the patch test behind the ear, which appeared the day after the hair was dyed. There was no irritation resulting from the actual use of the dye.

6. One woman had used the dye six times without any complaint. She reported that she had an irritation of the scalp after the seventh time, despite the claim that the patch test had been negative. At the time of the examination one week later there were no signs of dermatitis remaining. Although advised not to do so, this woman used the dye again, but she had no ill-effects.

After dyeing of their hair with this home hair coloring, 234 women were observed by two other dermatologists. They found no allergic reactions but did note 20 subjects with slight excoriations of the scalp following the use of the dye. These excoriations soon disappeared and did not recur upon continued use of the dye. They noted 23 instances of excoriation among the 234 women before the dye was used.

The home hair dye has now been commercially available for more than one year, and about 10,000,000 packages have been sold by the company that first placed it on the market. The company has received less than 125 letters from the users stating that they have had skin irritation from use of the dye. This is 1 complaint for 80,000 packages sold.

Upon investigation many of the complaints proved not to be due to the dye at all, and those due to the dye were mostly of excoriations on the scalp, such as those previously described. When actual dermatitis had occurred, no preliminary patch test had been made or the test had been improperly made. In 50 of the cases small "nuisance" settlements were made. So far, no cases have reached legal adjudication, although several are pending. Some of the alleged cases of dermatitis that were investigated showed evidence of overtreatment with topical applications of strong antiseptics, sulfonamide compounds, antibiotics, antihistaminics, anesthetics, etc. In this connection, the physician should bear in mind that dermatitis from dyes is not an infection but an allergic contact dermatitis and that it should receive palliative treatment, such as wet dressings of dilute aluminum acetate solution or of boric acid solutions when the dermatitis is acute. When the swelling and oozing, if present, subside, then mild ointments, such as zinc oxide ointment, are of value. Cases of dermatitis alleged to be caused by hair dyes are potential cases for litigation and should not be treated by topical applications which may themselves cause local or systemic reactions. Nor should uncomplicated dermatitis be treated either internally or externally with neutralizing chemicals, antiseptics, antibiotics, antihistaminics, hormones, etc., all of which may cause dermatitis and systemic manifestations that may be erroneously attributed to the paraphenylenediamine dyes.

SUMMARY

Since 1937, reported cases of dermatitis from paraphenylenediamine hair dyes have been rare despite the great increase in their use.

In the cases that have occurred, localized areas of allergic contact dermatitis were observed in hypersensitive persons.

The decrease is due to the following factors:

1. Care by the manfacturers in the manufacture of the dyes to assure correct composition of the finished products in accordance with the formulas which have been proved to be safe by adequate investigation.

2. The availability and use of pure ingredients for manufacturing the dye.

3. The use of the prophetic patch test and trial usage tests before marketing of the dyes.

4. Careful packaging and detailed instructions for the use of the dyes in each package as prescribed and required by law.

5. Predyeing open patch tests by the consumer as required by law, the directions for performing the tests being contained in each package.

The method we describe of performing the open prophetic patch test with hair dyes has proved itself in the case of a new hair dye for home use.

CONCLUSION

The use of modern paraphenylenediamine hair dyes as now regulated by law is not attended by any undue hazard.

CAT-SCRATCH FEVER

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THE CLICHÉ, "There is nothing new under the sun," is proved by repetition in medicine. New entities are recognized and reported constantly. Yet identical cases have been observed and perhaps recorded previous to the "original" report. The voluminous medical literature makes it impossible for an author claiming priority to check all previous reports of a given condition. Furthermore, identical cases may be described under different names, so that even the *Quarterly Cumulative Index Medicus* will not reveal such reports.

A case in point is cat-scratch fever. According to Greer and Keefer,[1] their article in April, 1951, was the first report of this entity in the English literature. However, they state that Foshay [2] called their attention to this disease and had prepared a diagnostic antigen for skin testing. They also point out that Debré, Lamy, Jammet, Costil, and Mozziconacci [3] had described this condition in the French literature, mentioning 10 cases but presenting only 1 in detail. Looking through the *Current List of Medical Literature* of the Army Medical Library, one is impressed by the number of articles on the subject in the European, and especially the French, literature.

Within one year, 1945-1946, I saw four patients with cat-scratch fever. The condition in one of these (Case 2) was reported as "para-anthrax," since the viral nature of this condition was not recognized.[4] However, because of the bizarre but constant clinical picture, this patient is being reported on again, along with three others, to emphasize the clinical picture for the dermatologist.

REPORT OF CASES

CASE 1.—Mrs. A. McK., a 37-year-old white woman, was first seen on Nov. 21, 1945. She stated that two months previously, a "lump" had developed on her right wrist after a cat scratch in Rhode Island. This had persisted with comparative remissions and relapses in the amount of inflammation. On examination, she presented a firm, erythematous papule on her right wrist. There was some crusting over the lesion.

She was next seen on Dec. 4, 1945. She had gone to Carmel, Calif. On Dec. 1, tender lymphadenopathy had developed in the right epitrochlear and axillary regions. This was accompanied with general malaise and a temperature elevation to 103 F. by mouth. She had been

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1. Greer, W. E. R., and Keefer, C. S.: Cat-Scratch Fever: A Disease Entity, New England J. Med. **244**:545 (April 12) 1951.

2. Foshay, L., cited by Greer and Keefer.[1]

3. Debré, R.; Lamy, M.; Jammet, M. L.; Costil, L., and Mozziconacci, P.: La maladie des griffes de chat, Bull. et mém. Soc. méd. hôp. Paris **66**:76 (Jan. 20) 1950.

4. Epstein, E.: Para-Anthrax: Infection with Organisms Resembling Bacillus Anthracis, Arch. Dermat. & Syph. **57**:664 (April) 1948.

hospitalized and had received 600,000 units of penicillin intramuscularly over a period of three days without benefit. Her urinalysis had revealed only normal findings. There was a leucocyte count of 14,200, with 74% polymorphonuclear leucocytes. The patient was placed on a program of bed rest, forcing of fluids, and administration of 6 gm. of sulfadiazine per day.

There was comparatively little benefit from this regimen. On Dec. 12, a pipestem lymphangitis developed in the right axilla. On the same date, intradermal tests were done with Frei antigen, histoplasmin, coccidioidin, and tuberculin (second strength). All reactions were negative, except for a mildly positive reaction to the tuberculin. Repeated blood counts gave results similar to those mentioned above, except for an eosinophilia, the eosinophiles ranging from 5 to 8%. Agglutination tests for tularemia gave negative reactions in strengths of 1:20 through 1:1,280. The Wassermann and Kline reactions of the blood were negative.

On Dec. 20, she was operated on by Dr. Louis Lohse. The epitrochlear and axillary lymph nodes were found to be necrotic. Bacteriologic studies revealed the following: In a Gram stain of material from a lymph node no organisms were seen; aerobic culture yielded Staphylococcus aureus (beta hemolytic); yeast forms (probably a contaminant) were present; on anaerobic culture Staph. aureus was seen; on appropriate staining of the lymph node material, no acid-fast bacteria were noted. The histologic findings were the same as those described in Case 2, except that there was more extensive necrosis, and inflammatory changes were present.

By Jan. 5, the patient was well.

Case 2.—F. M. S., a 15-year-old white schoolgirl, was referred to me on Dec. 1, 1945. She stated that she had been scratched on the left wrist by a stray cat three months previously. About one week later a small papule developed in the area of the scratch, which slowly healed without significant treatment. Two weeks before examination a large mass developed in her left epitrochlear region, and a few days later a similar swelling appeared in her left axilla. At about the same time she noted a daily rise in temperature, reaching 103 F. (oral). This had slowly subsided, so that by Dec. 1 she had only an afternoon rise to 99.5 F. daily. She had taken 20 tablets of sulfadiazine, 0.5 gm. each, about one week prior to examination, without benefit. The patient presented massive lymphadenopathy involving her left epitrochlear and axillary regions. The nodes were firm and mildly tender. The overlying skin was not discolored. There was no evidence of fluctuation. There was a healed ecthymatous lesion on her left wrist. No masses were felt in her breasts. The other lymph nodes were not enlarged. The liver and spleen were not palpable. The results of the remainder of the examination were normal.

Laboratory Observations.—The observations on two urinalyses were not remarkable. A blood cell count was done on Dec. 11, with the following results: The hemoglobin concentration was 15.3 gm. per 100 cc. (90%), the erythrocyte count was 4,720,000 per cubic millimeter, and the color index was 0.95. The white blood cell count was 11,000 per cubic millimeter, with 72% polymorphonuclear leucocytes, of which 24% were stab forms and 48% were segmented, 1% eosinophiles, and 27% lymphocytes. The red blood cells were grossly normal. The blood cell count was repeated six days later, with similar observations. The white blood cell count was now 12,400 per cubic millimeter, with 74% polymorphonuclear leucocytes; 20% of these cells were stab forms, the other 54% being segmented. There were also 19% lymphocytes, 1% monocytes, 3% eosinophiles, and 3% basophiles.

The reactions to Kolmer, Kahn, and Kline tests were negative. Reactions to serologic tests for tularemia were negative in dilutions of 1:20 through 1:1,280 on Dec. 1 and again on Dec. 13. The sedimentation rate was rapid. By the Linzenmeier method there was a fall of 18 mm. in 21 minutes. The Cutler method of study gave the following results:

Min.	Mm.	Min.	Mm.
10	3	40	24
20	16	50	25
30	22	60	25

Reactions to intradermal tests with old tuberculin (first and second strengths), histoplasmin, coccidioidin, and Frei antigen were negative.

Histologic studies of excised tissue from the epitrochlear and axillary nodes revealed inflammatory and necrotic changes. The germinal centers were hyperplastic and edematous. The capsule was acutely inflamed. In some areas a large zone of necrosis could be seen. This

was composed of cellular debris and amorphous eosinophilic material. Fibrosis was prominent near the periphery of these necrotic areas. No giant cells were noted. There was no evidence of a lymphoblastomatous process.

Bacteriologic Studies.—Material was obtained at operation under sterile technique from both the epitrochlear and the axillary areas. No bacteria were noted on stained slides made from this material. Stains for acid-fast bacteria disclosed none of these organisms. Potassium hydroxide preparations failed to reveal the presence of any fungi. Cultures in simple broth showed no growth after 24 hours, but in 48 hours a pure culture of a large rod was observed. It grew satisfactorily in anaerobic cultures. There was no growth on Sabouraud's medium.

The organism was observed to be a Gram-positive large slender rod growing singly and in chains of varying length. It was definitely motile. The ends were rounded. No capsule was noted. Spores formed both equatorially and subterminally. Studies showed it to be an aerobe with facultative anaerobic characteristics. It produced acid, but no gas, in glucose, sucrose, and maltose. Growth in broth resulted in slight turbidity and formation of sediment. In milk, an alkaline reaction was produced without clotting. On a gelatin stab, slow liquefaction resulted, with the surface membrane adhering to the sides of the tube. The rod produced beta-type hemolysis on blood agar. There was slight liquefaction of blood serum.

It was felt that from these characteristics the organism could best be classified as Bacillus anthracoides.

Treatment and Course.—The patient was hospitalized from Dec. 10 to 24. Among the therapeutic measures tried, without benefit, were administration of penicillin, given intramuscularly in doses of 25,000 units every three hours for a total dose of 1,400,000 units, sulfadiazine, 1 gm. every four hours for a total of 70 gm., and roentgen rays, at 120 kv. filtered through 3 mm. of aluminum for a total dose of 185 r, infrared irradiation, and use of hot compresses.

On Dec. 19 it was decided to explore the axillary mass. Dr. Maurice Zeff performed a biopsy and observed that the outer portion of the node was firm, but the central portion was necrotic. The organism described previously was isolated from the central area. Three days later the epitrochlear mass became fluctuant, and it was removed on Dec. 22. At operation the node was seen to be necrotic and the capsule destroyed. It was necessary to remove the node piecemeal.

While in the hospital, the patient had an intermittent afternoon fever, the temperature rising as high as 100.4 F. (oral). By Dec. 13, the peaks had dropped to 99.6 F. After the second operation the temperature became normal. After this, recovery was uneventful and complete. All signs of inflammation had completely subsided by Jan. 20, 1946.

Case 3.—H. J., a 36-year-old white man, was seen on Dec. 13, 1945. The patient had suffered multiple cat scratches on his left hand two weeks previously. In addition, he presented a paronychia of his right index finger and a deep pustular lesion on the back of his neck. Apparently these were not related to the scratches. The latter looked clean. However, on examination, he presented a fairly large left epitrochlear lymph node which he had not noticed himself. The other lesions were treated with superficial roentgen-ray therapy and local applications. He returned five days later, and the superficial pyogenic lesions were improved. However, the left epitrochlear lymphadenopathy was slowly increasing. Unfortunately, the patient did not return for further observation.

Case 4.—J. G. R., a 24-year-old white man, entered the Veterans Administration Hospital, Oakland, Calif., on Nov. 1, 1946. Six weeks before entry, he had purchased a cat. This animal died of unknown causes one week later. Three weeks after this, the patient noted a lesion on his right lower leg that he thought was a "boil." This area was red and slightly tender. Three days later, he noticed a tender swelling in the right groin. He also had chills and throbbing headaches at about the same time. Two days before entrance to the hospital, he became aware of an eruption on his chest and abdomen. On examination, the patient presented an ecthymatous, indurated, erythematous lesion in the midportion of the right shin. There was a maculopapular eruption on his chest and back with some pustular changes. He also presented a large mass of firm, matted, tender lymph nodes in the right femoral region. On entry his temperature was 100.8 F. by mouth. The tentative diagnosis of the ward medical officer was tularemia or plague.

Blood-agglutination tests for tularemia and plague were negative. Inoculation of blood into laboratory animals gave negative results. The blood serologic tests were negative also. The blood count was within normal limits except for an eosinophilia (4%). Cultures of material obtained from the lymph nodes resulted in no growth. A dark-field examination of lymph node material showed no spirochetes of syphilis or relapsing fever.

During his stay in the hospital, the patient ran a remittent type of fever that slowly subsided; the temperature became normal by Nov. 23. On Nov. 12, characteristic lesions of erythema nodosum developed on his legs. By Dec. 2, the lymph nodes had become fluctuant and were drained. Recovery was complete by Dec. 21. There was no response to the injection of penicillin in doses of 30,000 units every three hours.

COMMENT

Cat-scratch fever is believed to be due to a virus infection. The clinical picture is such as to suggest that it is produced by a micro-organism. However, as demonstrated in this series, the results of conventional bacteriologic studies are not constant. Unfortunately, virus studies were not performed. The positive skin test is said to resemble the Frei reaction. However, similar reactions are seen in many bacterial and mycotic infections.

The clinical picture is the most interesting feature. So far, most cases have followed a cat scratch, or at least exposure to cats. The original laceration may remain inactive or become echthymatous. One to 12 weeks later, the draining lymph nodes become enlarged. Case 3 suggests that this growth is gradual but does not reach the patient's attention until it becomes massive. These nodes may attain gigantic proportions. There is some tenderness. The overlying skin remains normal until late in the course of the condition. The nodes eventually become fluctuant, and drainage reveals that they are necrotic. The amount of purulent matter was comparatively small at the time that surgical exploration was done in these cases.

Systemic signs and symptoms include mild fever and general malaise. Cutaneous lesions may appear and be classified clinically as erythema multiforme or erythema nodosum.

Laboratory findings are not characteristic. Mild leucocytosis and increased sedimentation rate may be noted. Eosinophilia was demonstrated in Cases 1 and 4. It may have been present in others. Routine bacteriologic studies may reveal a number of organisms. The cultures have varied from being sterile to showing streptococci and staphylococci to yielding B. anthracoides. The histologic picture of the involved nodes reveals central necrosis, inflammation, and fibrosis.

The disease is thought to be self-limited. However, the course is apt to be stormy. In the three cases that I followed to recovery, surgical intervention was necessary and curative. Aureomycin, terramycin, etc., have been suggested as being of benefit and should be tried before surgical intervention.[5]

In summary, the impressive features are (1) the preceding cat scratch with comparatively little evidence of local inflammation, (2) the long incubation period, (3) the gigantic lymphadenopathy, and (4) the necrosis of the lymph nodes.

SUMMARY

Four cases of cat-scratch fever are reported. The clinical picture, laboratory findings, treatment, and etiology are discussed.

5. Lang, H. L.: Cat-Scratch Fever, J. Pediat. **39**:431 (Oct.) 1951.

TREATMENT OF SUPERFICIAL MYCOLOGICAL INFECTIONS WITH A NEW ANTIFUNGAL AGENT

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WE HAVE recently reported our experiences with a new antifungal agent, 2-dimethylamino-6-(beta-diethylaminoethoxy) benzothiazole (asterol®) dihydrochloride, in tinea capitis of the anthropophilic type.[1] The results of treatment in the 72 patients presented were so gratifying, even in the children whose parents contributed little cooperation, that we have since adopted the use of asterol® dihydrochloride as a routine measure in patients with ringworm of the scalp.

When Stritzler and his associates[2] reported their encouraging results with asterol® dihydrochloride in tinea of the glabrous skin and the nails, we decided to extend the evaluation of the new drug to patients with superficial fungous infections other than tinea capitis.

At this writing, we have collected adequate data to report our observations on asterol® dihydrochloride treatment in another group of patients with ringworm of the scalp, in a group with moniliasis, and in one with tinea versicolor. Therefore, the observations to be presented are divided into three phases, the first recording observations on patients with tinea capitis of the Microsporum audouini type treated since the formulation of our original article,[1] the second reporting results in infections due to Candida albicans, and the third presenting our experiences with treatment of tinea versicolor.

TINEA CAPITIS

Sixty-one patients, in all of whom M. audouini was culturally determined as the causative organism, were studied. In the majority of these the disease was of considerable severity, with involvement of disseminated patches. There were 46 boys and 15 girls, ranging in age from 3 to 12 years (average age, 8 years). The therapeutic and prophylactic regimen was essentially the same as that employed in our first series.

The hair was clipped short initially and at weekly intervals. Manual epilation was not regularly employed but was done in the very severe cases. Five per cent asterol® dihydrochloride was applied twice daily; the tincture was sprayed over the

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1. Edelson, E.; Craster, C., and Haskin, A.: Evaluation of a New Drug for Topical Therapy of Tinea Capitis, A. M. A. Arch. Dermat. & Syph. **64**:444-448 (Oct.) 1951.

2. Stritzler, C.; Fishman, I. M., and Laurens, S.: Treatment of Superficial Fungus Infections with a New Antifungal Agent, Tr. New York Acad. Sc. **13**:31-37 (Nov.) 1950.

entire scalp to "thorough wetness" every morning, and the ointment was applied plentifully at bedtime. Both medication forms were gently massaged into the scalp. Shampooing of the head every other night, preceding the application of the ointment, was prescribed.

As in our previous series, a patient was pronounced cured after six consecutive negative Wood-light examinations at weekly intervals. Our present results are recorded in Table 1.

The time of treatment required for the first Wood-light negativity in the group of cured patients ranged from 3 to 15 weeks (average, 8 weeks).

The time of treatment for the improved children ranged from 3 to 11 weeks (average, 9½ weeks), and that for the unimproved patients from 4 to 21 weeks (average, 14 weeks).

TABLE 1.—*Results in Tinea Capitis Due to M. Audouini Treated with Five per Cent Asterol® Dihydrochloride*

No. of Patients	No. Cured	No. Improved	No. Unimproved
61	42	12	7

TABLE 2.—*Summary of Results in Fifty-Three Patients with Moniliasis Treated with Five per Cent Asterol® Dihydrochloride*

Diagnosis or Area of Involvement	No. of Patients	No. Cured	No. Improved	No. Unimproved
Paronychia	16	11	2	3
Onychomycosis	6	3	1	2
Interdigital spaces	10	7	2	1
Commissurae oris	6	3	2	1
Axillae	2	1	..	1
Inframammary region	3	2	1	..
Inguinocrural region	1	1	..	..
Perianal region	4	3	..	1
Extremities and buttocks	4	4	..	..
Canthi	1	1	..	..
Totals	53	36	8	9

In 13 children, or 21.3%, folliculitis or kerion-like reaction developed. Ten of these patients were pronounced cured. Thus, of the 42 cured patients, 10 went through an inflammatory phase before they progressed to cure. In these, the average period of treatment to attain Wood-light negativity was six and one-half weeks, as contrasted with eight weeks in those children who were cured but in whom an inflammatory reaction did not develop.

MONILIASIS

Eighty-one patients with a clinical diagnosis of moniliasis were treated with asterol® dihydrochloride. However, only the 53 patients whose cultures were positive for C. albicans are included in this evaluation.

The distribution of the areas of involvement in these 53 patients can be seen in Table 2. The treatment plan employed in the various groups will be detailed in the discussion on the individual disease entities.

With the exception of the patients with nail involvement, those listed as cured, in general, were clinically cured. However, patients with onychomycosis were pronounced cured only if a clinical cure was corroborated by cultures showing no C. albicans. Of the total group of 53 patients, 36 were cured, 8 were improved, and 9 were not improved.

As is seen in Table 3, which shows the distribution of those with the chronic and with the acute disease, the cure rate among patients with the acute disease was slightly higher than in those chronically afflicted.

Paronychia.—There were 16 patients who had paronychial infections without nail involvement. In seven of these, the terminal phalanx of only one finger was afflicted, and in nine there were multiple paronychial infections (two to seven fingers). After soaking of the affected phalanges in boric acid solution and thorough

TABLE 3.—*Distribution of Fifty-Three Patients Having Chronic and Acute Moniliasis Treated with Five per Cent Asterol® Dihydrochloride and Summary of Results*

	Chronic Disease				Acute Disease			
Diagnosis or Area of Involvement	Total No. of Patients	No. Cured	No. Improved	No. Unimproved	Total No. of Patients	No. Cured	No. Improved	No. Unimproved
Paronychia								
Single infection	5	4	..	1	2	2	..	..
Multiple infection	7	4	2	1	2	1	..	1
Onychomycosis	6	3	1	2	..	..	..	..
Interdigital spaces	6	4	1	1	4	3	1	..
Commissurae oris	4	2	1	1	2	1	1	..
Axillae	2	1	..	1	..	..	..	..
Inframammary region	2	1	1	..	1	1	..	..
Inguinocrural region	1	1	..	..	..	..	..	..
Perianal region	3	3	..	..	1	..	..	1
Extremities and buttocks	1	1	..	..	3	3	..	..
Canthi	1	1	..	..	..	..	..	..
Totals	38	25	6	7	15	11	2	2

drying, 5% asterol® dihydrochloride ointment was applied three times daily with a cotton-tipped applicator so that the preparation was worked well under the nail folds and covered the entire area of infection. The use of soap was forbidden, and the patients were told to use glove protection whenever it became necessary to handle wet objects. Table 2 shows that 11 patients were cured, 2 were improved, and 3 remained unimproved. It appears from Table 3 that the cure rate in the patients with a single paronychial infection was higher than in those with multiple sites of involvement. In the former, the average time required for cure of chronic and acute infections was 26 and 21 days, respectively. In the patients with multiple sites of involvement, the time required for cure of chronic and acute infections was 33 and 26 days, respectively. In general, improvement was noticeable within a few days after institution of asterol® dihydrochloride treatment.

Onychomycosis.—Of the six patients with onychomycosis, four showed paronychial involvement, but two did not. In five patients the fingernails and in one patient the toenails were affected. One to five nails were involved in the individual patients. To reduce the thickness of the nail plates, these were sanded with emery board at frequent intervals, and the resulting dust was removed with alcohol. Five per cent asterol® dihydrochloride ointment was applied at least twice daily. In

the patients with paronychial involvement, the regimen included sanding of the nails and treatment of paronychial areas and the nails as outlined above.

Our criteria for cure were complete regrowth of a smooth nail of normal appearance and negative cultural findings. As is seen in Table 2, three patients were cured; one was improved, and two were not improved. In general, improvement became noticeable within 8 weeks, and the average time required for cure was 31 weeks. If there was no improvement after three months, as in the two patients classified as not improved, treatment with asterol® dihydrochloride was discontinued.

Interdigital Moniliasis.—Of the 10 patients with moniliasis of the interdigital spaces, the finger webs were affected in 8 and the toe webs in 2. In the former, after application of wet boric acid dressings, asterol® dihydrochloride ointment was administered twice daily by slight massage. The two patients with toe-web involvement sprinkled asterol® dihydrochloride dusting powder on their feet and in their socks in the morning and used asterol® dihydrochloride ointment at bedtime. Lamb's wool, thinly packed between the toes, helped to keep the intertriginous areas dry.

As is seen in Table 2, seven patients were cured; two were improved, and one remained unimproved. The average time required for cure was 15 days. The two patients classified as improved were actually lost from observation after they had shown definite improvement on their last reexamination. For the unimproved patient, treatment had been continued for three weeks.

Monilial Perlèche.—In all six patients with moniliasis of the labial commissures, an overhanging upper lip causing collection of saliva in the commissural sulci with subsequent maceration was a predisposing factor. Asterol® dihydrochloride ointment was applied three times daily. General measures included the substitution of sodium bicarbonate and salt for tooth paste or powder and mouth washings with saline solution after meals. The patients were advised to refrain from chewing gum and tobacco, when such habits existed. Dietary measures were directed toward elimination of spices or dishes which might irritate the labial regions. Similarly, the patients were told to ingest tepid food only.

As is seen in Table 2, three patients were cured, two were improved, and one was not improved. The average time required for cure was 10 days. Obviously, recurrences cannot be prevented in this type of lesion unless the predisposing deformity is corrected. One of the two improved patients was lost from observation after she had shown remarkable improvement eight days following institution of therapy. The patient with chronic perlèche who showed no improvement (Table 3) had uncontrollable diabetes, poorly fitting dentures, and commissural pockets. He refused to have his dentures corrected, as did the patient with chronic commissural lesions who was classified as improved.

Axillary, Inframammary, Inguinocrural, and Perianal Moniliasis.—There was a total of 10 patients with monilial infections involving the axillary, inframammary, inguinocrural, or perianal regions. These patients are grouped together because the therapeutic measures were similar in all instances. Treatment consisted of use of wet dressings with boric acid solution twice daily, followed by thorough drying. Asterol® dihydrochloride ointment was applied nightly, and asterol® dihydrochloride dusting powder was applied every morning and once in the course of the day. The patients were advised not to use soap on the involved areas and to refrain from employing deodorants and other cosmetics on the lesions or in their proximity.

They were also told to avoid tight-fitting or abrasive clothes and to eliminate activities causing excessive perspiration. Dietary measures were directed toward reduction of intake of sweets.

As is seen in Table 2, results in these patients with intertriginous moniliasis were as follows: One patient of the two with axillary involvement and two patients of the three with lesions in the inframammary region were cured. In one patient, inguinocrural moniliasis of considerable severity with maceration and superficial fissuring was cleared as was the infection in three patients of the four with perianal involvement. The cultures for the last three cured patients became negative for C. albicans, but the pruritus subsided completely in only one of them. The cures of the seven patients with intertriginous moniliasis were obtained in two to four weeks. In the unimproved patient with axillary moniliasis dermatitis venenata developed nine days after initiation of asterol® dihydrochloride medication. This abated with discontinuance of treatment, to reappear on reexposure to the drug. The reaction subsided again shortly after withdrawal of the medication. A patch test done subsequently gave a positive reaction (2+) after 48 hours. The patient with bilateral inframammary involvement classified as improved was actually lost from observation. When she was last seen, 23 days after institution of asterol® dihydrochloride treatment, one inframammary area was cleared, and the corresponding lesion on the other side was almost completely gone. One patient with perianal moniliasis was lost from observation after use of asterol® dihydrochloride and other methods of treatment had failed completely.

TABLE 4.—*Results in Tinea Versicolor Treated with Five per Cent Asterol® Dihydrochloride*

No. of Patients	No. Cured	No. Improved	No. Unimproved
11	8	3	0

Moniliasis on Extremities and Buttocks.—The sites of involvement in the four patients placed in this category were the palmar surfaces and finger webs, the forearms, the thighs, and the buttocks, respectively. In all instances, asterol® dihydrochloride ointment applied twice daily was attended with complete clearing of the lesions. This was accomplished in the patient with palmar and finger-web involvement in four weeks and in the three other patients in an average of 13 days.

Canthal Moniliasis.—The patient with chronic moniliasis of both external canthi was a 36-year-old male machinist without contributory seborrheic or constitutional illness. He used asterol® dihydrochloride ointment sparingly three times daily while continuing at his work. Three days after institution of treatment with this drug, mild bilateral conjunctivitis developed, but treatment was continued for 13 days, when his canthi were completely clear. The conjunctivitis abated with cessation of treatment with asterol® dihydrochloride ointment. There was no recurrence of the moniliasis for the past three months, the period of observation.

TINEA VERSICOLOR

Table 4 summarizes our results in tinea versicolor on treatment with 5% asterol® dihydrochloride.

Asterol® dihydrochloride ointment was applied twice daily. A cleansing bath was advised before the night application. In those instances in which the ointment could not be applied during daytime, asterol® dihydrochloride tincture was sprayed on the lesions in the morning. After evaporation of the alcohol, asterol® dihydrochloride dusting powder was applied.

As is seen in Table 4, eight patients were clinically cured, and three, improved. Wood-light negativity in the cured patients was attained in 7 to 36 days. Two of the subsequently cured patients complained of a slight burning and tingling sensation after they had used the ointment five and seven days, respectively. Asterol® dihydrochloride dusting powder was then substituted for the ointment in the morning, and this relieved these patients from their paresthesias. The three patients classified as improved were actually lost from observation after they had all shown marked improvement when last reexamined in the clinic after 10, 11, and 13 days of treatment. In fact, there was not one patient who failed to show prompt improvement.

COMMENT

The results with asterol® dihydrochloride in the present group of 61 patients with ringworm of the scalp due to M. audouini are in very good agreement with our previously reported observations on a similar group of 71 patients. In the original series asterol® dihydrochloride therapy produced Wood-light negativity in 66.6% of the patients. Definite improvement was obtained in 23.7%, while 9.7% remained unimproved.[1] In the present group the cure rate was 68.9%; the incidence of improvement was 19.7%, and 11.5% remained unimproved.

We feel certain, on the basis of these observations, that asterol® dihydrochloride is a very satisfactory agent in combating tinea capitis of the highly resistant M. audouini type and that it compares very favorably with other medicaments available for this purpose. Up to the time we introduced asterol® dihydrochloride into our armamentarium, more than a year ago, we had a four months' backlog of patients awaiting x-ray epilation for tinea capitis. Since we have been using asterol® dihydrochloride therapy, the patient requiring x-ray epilation is the unusual one.

In discussing a paper recently presented by Ravits [3] on the merits of asterol® dihydrochloride in dermatomycoses, Appel [4] described very interesting experiments which clearly demonstrate the value of asterol® dihydrochloride in eradicating M. audouini. He reported that infected hairs extracted from children with tinea capitis of the anthropophilic type were rendered sterile by immersion into 2% tincture of asterol® dihydrochloride for several hours. Since all hairs were carefully rinsed before they were planted on Sabouraud's agar, the absence of M. audouini in cultures suggests a fungicidal effect of the drug. These very gratifying in vitro observations are in keeping with our excellent clinical results.

The rate of success in both our series approximates the results reported by Stritzler and associates,[2] who, in a group of 61 patients with tinea capitis of the anthropophilic type treated with asterol® dihydrochloride, attained Wood-light negativity in 43, or 70.4%. Sullivan and Bereston [5] have recently reported a cure

3. Ravits, H. G.: Treatment of Superficial Dermatomycoses with Asterol® Dihydrochloride, J. A. M. A. **148**:1005-1007 (March 22) 1952.

4. Appel, B., in discussion on Ravits.[3]

5. Sullivan, M., and Bereston, E.: Evaluation of Topical Remedies for Tinea Capitis in 800 Cases Due to M. Audouini, read before the Section on Dermatology and Syphilology at the 100th Annual Session of the American Medical Association, Atlantic City, June 14, 1951.

rate of only 40% in ringworm of the scalp treated with this drug. In presenting their paper, these workers offered as possible explanation for their less favorable results the fact that they used asterol® dihydrochloride in a concentration of 2%, whereas other students employed 5% preparations. This is in harmony with our own observations that 5% asterol® dihydrochloride ointment and tincture yield much better results than the preparations containing only 2% of the active ingredient which we used initially.

Our results with asterol® dihydrochloride in the 53 patients with C. albicans infections and in the 11 patients with tinea versicolor were most gratifying. We agree with Stritzler and associates,[2] who commented that monilial infections and tinea versicolor respond more favorably to asterol® dihydrochloride than to other medicaments. The cure rate of 67.9% recorded in our series of moniliasis and that of 66.6% reported by the other workers [2] are almost identical.

While our cure rate in tinea versicolor is lower than that scored by Stritzler, it must be remembered that our three patients with a diagnosis of tinea versicolor classified as improved had actually been lost from observation. We feel that in monilial infections and in tinea versicolor asterol® dihydrochloride offers the greatest assurance for a rapid recovery.

SUMMARY AND CONCLUSIONS

Sixty-one patients (46 boys and 15 girls), ranging in age from 3 to 12 years, with tinea capitis due to Microsporum audouini were treated with 2-dimethylamino-6-(beta-diethylaminoethoxy) benzothiazole (asterol®) dihydrochloride. Forty-two children, or 68.9%, were cured on the basis of six weekly negative Wood-light examinations; 12 children, or 19.7%, were improved, and 7, or 11.5%, showed no improvement. These results are in perfect agreement with those obtained in a previous series of 72 patients.

In addition, 53 patients with a clinical diagnosis of moniliasis and cultures showing Candida albicans were treated with asterol® dihydrochloride. Thirty-six patients, or 67.9%, were cured; eight, or 15.1%, were improved, and nine, or 17%, remained unimproved. Patients with onychomycosis were pronounced cured only after complete regrowth of a smooth nail or normal appearance and cultures revealing no C. albicans. In general, patients with other than nail involvement listed as cured were clinically cured. The series is classified according to the area of involvement, and the method of treatment in each group is described.

Finally, 11 patients with tinea versicolor were treated with asterol® dihydrochloride. Eight of these were cured, and three were improved.

In only 1 patient of the total 125 presented did a sensitivity reaction develop. Asterol® dihydrochloride was found highly effective in treatment of tinea capitis due to M. audouini, in moniliasis, and in tinea versicolor.

The asterol® dihydrochloride preparations used in this study were supplied by Dr. Leo A. Pirk, of Hoffmann-La Roche, Inc., Nutley, N. J. Dr. Pirk and Dr. Emanuel Grumberg aided us in this work.

STERNAL MARROW FINDINGS IN VARIOUS DERMATOSES

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HUMAN marrow has been the subject of intensive clinical investigation since Arinkin [1] introduced the sternal puncture in 1929. The importance of this procedure in the study of blood dyscrasias [2] has been well established, and its value in the study of cancer,[3] renal disease,[4] hepatic disease,[2a] and some of the systemic diseases [5] has been carefully explored.

Reports on the marrow findings in the leukemias [6] and in the lymphoblastomata (malignant lymphomata [7]) are of considerable interest to the dermatologist because

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1. Arinkin, M. I.: Die intravitale Untersuchungsmethodik des Knochenmarks, Folia hæmat. **38**:233-240, 1929.

2. (*a*) Leitner, S. J.: Bone Marrow Biopsy: Haematology in the Light of Sternal Puncture, New York, Grune & Stratton, Inc., 1949. (*b*) Custer, P.: An Atlas of the Blood and Bone Marrow, Philadelphia, W. B. Saunders Company, 1949.

3. Jonsson, U., and Rundles, R. W.: Tumor Metastases in Bone Marrow, Blood **6**:16-25, 1951.

4. Callen, I. R., and Limarzi, L. R.: Blood and Bone Marrow Studies in Renal Disease, Am. J. Clin. Path. **20**:3-23, 1950.

5. Kracke, R. R.: Bone Marrow Studies, Editorial, Am. J. Clin. Path. **20**:93-94, 1950.

6. (*a*) Welch, G. E.: The Bone Marrow in Diseases of the Leukopoietic System, New Orleans M. & S. J. **99**:21-33, 1946. (*b*) Hubler, W. R., and Netherton, E. W.: Cutaneous Manifestations of Monocytic Leukemia, Arch. Dermat. & Syph. **56**:70-89, 1947. (*c*) Deenstra, H., and van Ijzeren, H.: Monocytic Leukemia: A Case Report of Naegeli-Type, Acta haemat. **1**:55-59, 1948.

7. (*a*) Cooper, T., and Watkins, C. H.: An Evaluation of Sternal Aspiration as an Aid in Diagnosis of Malignant Lymphoma, Blood **4**:534-539, 1949. (*b*) Wayson, J. I., and Weidman, F. D.: Aleukemic Reticulosis, an Additional Member of the Group of So-Called Cutaneous Lymphoblastomas, Arch. Dermat. & Syph. **34**:755-774, 1936. (*c*) Steiner, P. E.: Hodgkin's Disease: Incidence, Distribution, Nature and Possible Significance of Lymphogranulomatous Lesions in Bone Marrow; Review with Original Data, Arch. Path. **36**:627-637, 1943. (*d*) Hynes, M.: Sternal Puncture, Lancet **1**:1373-1379, 1939.

of the appreciable incidence and the importance of cutaneous involvement in these conditions. The changes in the marrow in generalized sarcoidosis (Schaumann's disease [8]), in malignant melanoma with metastases,[9] and in congenital hypoplastic anemia associated with multiple skeletal defects and pigmentation of the skin (Fanconi syndrome [10]) are likewise of great interest to the dermatologist, since cutaneous involvement may be the principal or initial manifestation in these diseases. The recent discovery by Hargraves [11] of the diagnostic L. E. cell in the bone marrow of patients suffering from acute lupus erythematosus disseminatus and the brilliant investigations of the L. E. phenomenon by Haserick and Bortz [12] have been foremost among the achievements in the past few years by investigators in the dermatologic field. The importance and significance of these studies have been recognized by internists and hematologists as well.[13]

Reports dealing with the results of marrow studies in diseases limited to or principally involving the skin have been few. Mezzadra and Carli [14] examined the sternal marrow of patients with psoriasis, lupus vulgaris, and bullous eruptions. They found that, on the whole, the bone marrow was normal in these conditions. Bessone [15] searched for diagnostic changes in the marrow of patients with idiopathic hemorrhagic sarcoma (Kaposi's sarcoma), and a number of investigators [16] have examined the marrow in mycosis fungoides (granuloma fungoides). De Graciansky and Paraf [17] attempted to correlate the findings in the circulating blood with those in the marrow in *les hématodermies*. They failed to find a characteristic deviation either in the blood or in the marrow in *les granulomatoses* (mycosis fungoides and Hodgkin's disease).

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8. (*a*) Dressler, M.: Über einem Fall von Splenomegalie, durch Sternalpunktion als Boecksche Krankheit verifiziert, Klin. Wchnschr. **17**:1467-1471, 1938. (*b*) Gormsen, H.: The Occurrence of Epithelioid Cell Granulomas in Human Bone Marrow, Acta med. scandinav. (Supp. 213) **131**:154-164, 1948.

9. Dubois-Ferriere, H.: La moelle osseuse dans le mélanome malin, Helvet. med. acta **13**:319-322, 1946.

10. Estren, S.; Suess, J. F., and Dameshek, W.: Congenital Hypoplastic Anemia Associated with Multiple Developmental Defects (Fanconi Syndrome), Blood **2**:85-93, 1947. Poikiloderma congenitale as described by M. S. Thomson (Poikiloderma Congenitale, Brit. J. Dermat. **48**:221-234, 1936) may be the same or a related condition.

11. Hargraves, M. M.; Richmond, H., and Morton, R. J.: Presentation of 2 Bone Marrow Elements: The "Tart" Cell and the "L. E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28, 1948.

12. Haserick, J. R., and Bortz, D. W.: Normal Bone Marrow Inclusion Phenomena Induced by Lupus Erythematosus Plasma, J. Invest. Dermat. **13**:47-49, 1949.

13. Dameshek, W., and Bloom, M. L.: Bone Marrow Examinations and the "L. E." Cell, Editorial, Blood **5**:101-103, 1950.

14. Mezzadra, G., and Carli, G.: Ricerche e osservazioni critiche sull'esame dello sternopuntato nel campo dermatologico, Haematologica **28**:363-402, 1946.

15. Bessone, L.: Bone Marrow in Kaposi's Disease, Dermosifilografo **17**:502-519, 1942.

16. (*a*) Lapiere, S., and de Weerdt, W.: L'aspect de la moelle osseuse dans le mycosis fungoide, Sang **13**:392-400, 1939. (*b*) Santoianni, G.: Primi risultati di ricerche in vivo sulla citologia del midollo osseo nel corso di alcune dermatosi, Riforma med. **52**:1727-1731, 1936. (*c*) Tzanck, A.; Dreyfuss, A., and Levy, S.: La ponction sternale dens le mycosis fungoïde, Sang **12**:110-112, 1938. (*d*) Tilley, R. F., and Smith, D. C.: Bone Marrow Changes in Mycosis Fungoides, J. Invest. Dermat. **14**:387-390, 1950.

17. de Graciansky, P., and Paraf, A.: Les corrélations médullo-sanguines dans les hématodermies et, en particulier, dans les granulomatoses, Semaine hôp. Paris **26**:2112-2121, 1950.

This study deals with the marrow findings in a wide range of dermatoses: some in which the cutaneous involvement is secondary to a blood dyscrasia, to a malignant lymphoma, or to a systemic disease; others in which the skin is the first or principal organ involved, and a number in which the pathologic process appears to be limited to the skin.

MATERIAL

The present report deals with studies begun in 1942 and carried out on 84 selected patients. Ambulatory as well as hospitalized patients were included. Every precaution was taken to exclude patients with coronary thrombosis or arteriosclerosis of the coronary arteries, in view of the rare fatality that may occur after sternal aspiration in such patients.[18] The extension of the investigations over the period of eight years was considered necessary to ensure adequate follow-up of the patients studied. An erroneous diagnosis would have been unavoidable for some patients had the follow-up period been shorter. This was particularly true of patients for whom a provisional diagnosis of mycosis fungoides or cutaneous lymphoblastoma had been made, since a number of the patients whose disease was first placed in this category subsequently made a complete recovery. Moreover, in some patients for whom the diagnosis of lymphoblastoma (malignant lymphoma[19]) could be made unequivocally, it was a matter of months or longer before the form or type of lymphoma could be designated.

The following cases were included:

Condition	No. of Cases
Chronic lymphatic leukemia	8
Monocytic leukemia (Naegeli type)	1
Leukemia or leukemoid reaction (lymphoid type)	2
Hemolytic anemia (familial type ?)	1
Hemolytic anemia (hereditary leptocytosis; Mediterranean anemia)	1
Thrombocytopenic purpura	1
Leucopenia of unknown causation	2
Polycythemia vera	2
Lymphosarcoma	4
Follicular lymphoblastoma (Brill-Symmers)	1
Malignant lymphogranuloma (Hodgkin's disease)	5
Mycosis fungoides	10
Lymphoblastoma, type undetermined	12
Idiopathic hemorrhagic sarcoma (Kaposi's sarcoma)	5
Malignant hemangioendothelioma of the skin	1
Sarcoidosis	4
Acute lupus erythematosus disseminatus	1
Subacute lupus erythematosus disseminatus	2
Chronic discoid lupus erythematosus	1
Exfoliative dermatitis	11
Eczematous and eczematoid eruptions (widespread)	7
Lichen planus	1
Total number of cases	84

PROCEDURE

Sternal aspiration of marrow rather than the bone marrow biopsy was used because of the relative simplicity of the technique, its applicability to ambulatory as well as hospitalized patients, and the opportunity it afforded to make repeated examinations when indicated. A Sleicher sternal aspiration needle was used, and the conventional technique of puncturing the sternum was employed. Approximately 1 ml. of marrow was aspirated, and direct smears

18. Meyer, L. M., and Halpern, J.: Death Following Sternal Puncture, Am. J. Clin. Path. **14**:247-248, 1944.

19. The term lymphoblastoma (malignant lymphoma) is used in the accepted sense to include lymphatic leukemia, lymphosarcoma (including reticulum-cell sarcoma of lymph nodes), malignant lymphogranuloma (Hodgkin's disease), follicular lymphoblastoma (Brill-Symmers disease), and mycosis fungoides.

were made on glass slides in the manner of making blood smears. The smears were fixed and stained with Wright's solution. Qualitative rather than quantitative examinations were made, because the amount of marrow that was collected varied, and also because the technique used for aspirating the marrow was not sufficiently standardized to make quantitative studies valid.

A total of 95 punctures was performed without mishap except for a dry tap on one occasion and a sufficient admixture of blood to invalidate the results in three specimens. Limarzi[20] has pointed out that in aspirating bone marrow cells, "one must of necessity withdraw peripheral blood (sinusoidal) at the same time." It was his experience as well as ours that on occasion the dilution may be so great as to leave only a few bone marrow cells on the film.

CASE MATERIAL AND RESULTS OF BONE MARROW STUDIES

The pertinent data and the results of bone marrow studies are presented in tabular form. The cases are grouped according to the final clinical and laboratory diagnoses.

Leukemia (Table 1).—The cases of chronic lymphatic leukemia had a number of interesting features in common in addition to the cutaneous involvement. First, the general condition of the patients was exceptionally good; second, the enlargement of the lymph nodes was not substantial except in one case, and, third, the spleen was not palpable in any of the cases. The hemograms, furthermore, were rather similar. The elevation in total leucocyte count was not high, the counts varying between 9,000 and 32,000 white blood corpuscles per cubic millimeter of blood (except for the leucopenia in Cases 3 and 8). The lymphocytes in the differential count likewise tended to be relatively low for this disease, numbering less than 72% in four of eight cases. The mature typical lymphocyte was the predominating form. Lymphoblasts were an inconspicuous feature (an occasional blast form was seen in Cases 4, 5, and 6). Immature or atypical cells in more than half the cases were relatively few. There was little or no anemia.

A total of nine aspirations was performed in eight cases of lymphatic leukemia. Lymphoid infiltration of the marrow was observed in seven cases, and there was no significant change in one case. The infiltrated marrow was cellular, and various types of white blood cells were seen. The most conspicuous change was the marked increase in the number of lymphocytes, which constituted approximately one-half to two-thirds of the nucleated cells. There was a corresponding reduction in the nucleated red blood cells and other nucleated forms. The lymphocytes were of either the small or the large variety. In some specimens there was a marked preponderance of fairly mature lymphocytes; in others, a smaller or larger proportion of the cells was immature.

A diagnosis of monocytic leukemia (Naegeli type) was made in Case 9, since immature cells of the granulocytic series and of the monocytic series were initially found in the peripheral blood. Later, however, the hemogram was typical of myelogenous leukemia, and chronic myelogenous leukemia was noted as the cause of death. The conflicting views pertaining to the nosology of the Naegeli or mixed form of monocytic leukemia have been reviewed by Hubler and Netherton.[6b]

A monocytic and granulocytic infiltrate was noted in the marrow in Case 9. Monocytes and monoblasts were present in considerable numbers. The cells designated as monocytes and monoblasts resembled somewhat abnormal myelocytes,

20. Limarzi, L. R.: Evaluation of Bone Marrow Concentration Techniques, J. Lab. & Clin. Med. **32**:732-740, 1947.

TABLE 1.—*Leukemia*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram*	Myelogram	Comment
1	47 F	1 yr.	Pruritus of scalp; lichenified eczema of the vulva	Enlarged	RBC, 4.1; hgb., 75%; WBC, 10,000-27,350; lymphocytes, av. 80%; many smudge forms; few atypical lymphocytes	Lymphoid infiltration	Eruption probably unrelated
2	54 M	17 yr.	Bullous leukemid and leukemic infiltration of skin and oral mucosa	Enlarged; histology: lymphatic leukemia or lymphosarcoma (small cell type)	RBC, 4.2; hgb., 81%; WBC, 14,350-22,400; lymphocytes, av. 70%; atypical and immature lymphocytes	Lymphoid infiltration	General condition good despite long duration
3	47 F	5 yr.	Moniliasis	Enlarged; histology: lymphatic leukemia	RBC, 4.8; hgb., 60%; WBC, 2,650-5,500; lymphocytes, av. 50%; few atypical lymphocytes	Lymphoid infiltration	Eruption unrelated
4	75 M	Few yr.	Generalized pruritus and leukemic infiltration	Enlarged	RBC, 4.0; hgb., 80%; WBC, 14,000-16,250; lymphocytes, av. 72%; many smudge forms; about 25% immature lymphocytes and a few blasts on one occasion	Lymphoid infiltration	.....
5	68 M	2 yr.	Pruriginous papular leukemid	Shotty	RBC, 4.8; hgb., 83%; WBC, 12,150-32,000; lymphocytes, av. 86%; few atypical lymphocytes and a few blasts seen on one occasion	Lymphoid infiltration	Condition unchanged 2 yr. later
6	60 F	3 wk.	Uriticaria and generalized pruritus	Enlarged	RBC, 4.1; hgb., 81%; WBC, 20,300-28,500; lymphocytes, av. 90%; few immature lymphocytes and occasional lymphoblast	Lymphoid infiltration	Herpes zoster subsequently and av. WBC 100,000 per cu. mm.
7	79 M	3 yr.	Leukemic infiltration	Enlarged; histology: lymphatic leukemia	RBC, 4.7; hgb., 90%; WBC, 9,150-21,000; lymphocytes, av. 64%; few atypical lymphocytes	No significant change	.....
8	67 M	6 mo.	Leukemic infiltration	Enlarged	RBC, 4.4; hgb., 80%; WBC, 3,200-6,800; lymphocytes, av. 76%; many atypical lymphocytes	1st: lymphoid infiltration 2d: appreciable reduction in no. of lymphoid cells following ACTH	Rapid resolution of the cutaneous lesions during first 2 wk. of ACTH therapy; failed to respond to further treatment with ACTH and other measures
9	54 M	8 mo.	Papular and nodular leukemic infiltrations	Enlarged	Representative early count: RBC, 4.4; hgb., 65%; WBC, 18,250; premyelocytes, 1; myelocytes, 7; metamyelocytes, 20; polymorphonuclear leucocytes, 22; basophiles, 2; lymphocytes, 20; monocytes, 28; many atypical monocytes	Monocytic and granulocytic infiltration	Conjunctival hemorrhages and leukemic infiltration of retina; died 1 yr. later of chronic myelogenous leukemia†

* RBC is red blood cell count in millions; WBC, white blood cell count; hgb., hemoglobin in per cent of normal, and av., average.
† Gouverneur Hospital, New York, supplied this report.

TABLE 2.—*Chronic Lymphatic Leukemia or Lympholeukemoid Reaction*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
10*	53 F	9 yr.	Exfoliative dermatitis; histology: lymphoblastoma	Enlarged; histology: dermatopathic lymphadenitis	RBC, 3.2; hgb., 71%; WBC, 11,950-29,100; lymphocytes, av. 55%; many smudge forms; few atypical lymphocytes	No significant change	Died of a terminal infection
11	50 M	6 mo.	Exfoliative dermatitis; 4 histologic examinations: 1st: compatible with lymphoblastoma 2d: lymphoblastoma 3d: undiagnosed condition of skin 4th: lymphoblastoma ?	Enlarged; histology: dermatopathic lymphadenitis	RBC, 4.8; hgb., 94%; WBC, 15,000-21,000; lymphocytes, av. 64%; few atypical lymphocytes; later counts were same except for lymphocytosis (average 69%) and many atypical lymphocytes	3 aspirations: 1st: granulocytic hyperplasia and occasional lymphoid cell 2d: granulocytic hyperplasia and occasional plasma cell 3d: eosinophilic hyperplasia and increase in lymphoid cells	Tip of spleen palpable on admission; hepatomegaly and splenomegaly 1 yr. later; enlargement somewhat marked 9 mo. later

* Gouverneur Hospital, New York, supplied this report.

and there was reasonable doubt whether they belonged to the granulocytic or the myelocytic series of white blood cells. In addition, there were the usual number and variety of myelocytes and a few myeloblasts. The number of nucleated red blood cells was approximately normal.

Chronic Lymphatic Leukemia or Lympholeukemoid Reaction (Table 2).—The term lympholeukemoid reaction (leukemoid reaction, lymphoid type) was used in the accepted sense, namely, to describe a hematologic picture closely resembling true chronic lymphatic leukemia. In both cases there was an absolute and relative lymphocytosis, with a varying number of atypical and immature lymphocytes. Lymphoblasts were not seen at any time in the peripheral blood.

A single aspiration of the marrow was made in Case 10. No significant change was noted. Three examinations were made in Case 11, the first, shortly after admission; the second, six months later, and the third, nine months after the second. A granulocytic hyperplasia [21] and occasional atypical lymphoid cells were seen in the first specimen. The nature of these occasional atypical lymphoid cells was not entirely clear. Their small number did not warrant a diagnosis of lymphoblastoma, but the possibility could not be entirely excluded. Furthermore, these cells were not encountered either on the second or on the third examination. The second sample of marrow showed a granulocytic hyperplasia and an occasional plasma cell. An eosinophilic hyperplasia [22] and an increase in lymphoid cells were observed in the third specimen. The lymphoid cells in the latter sample made up approximately one-third of the white blood cells, with large and small lymphocytes in equal numbers. Atypical and immature forms, however, were not seen.

Miscellaneous Group of Blood Dyscrasias (Table 3).—The conditions included in this category came to our attention because of an asociated cutaneous manifestation, e. g., chronic leg ulcer in hereditary leptocytosis (Cooley's anemia) in Case 13 or because of an unrelated dermatosis, viz., epidermoid carcinoma in situ of skin (Bowen's disease) with polycythemia vera (Case 8). In Case 12 it was difficult to say whether or not the erythroderma was causally related to the hemolytic process. Also in Cases 15 and 16 the cutaneous manifestations may or may not have been attributable to the chronic leucopenia. Because of the uncertainty it was considered better to include these cases among the blood dyscrasias than to list them as dermatologic entities.

An erythroblastic hyperplasia [23] and hemosiderosis [24] of the marrow were seen in both cases of familial hemolytic anemia. An erythoblastic marrow was likewise noted in one case of polycythemia vera, and a moderately cellular marrow in the other. In the case of essential thrombocytopenia purpura, the marrow was hyper-

21. In granulocytic hyperplasia there is a cellular marrow in which the cells of the granular (polymorphonuclear) series are abundant and in various stages of development. The hyperplasia of the granulocytes may be sufficiently marked to alter the myeloid/erythroid ratio.

22. The most conspicuous change is the increased number of eosinophilic cells, the majority of which are either eosinophilic myelocytes or eosinophilic leucocytes.

23. Erythroblastic hyperplasia is characterized by a cellular marrow in which there is a marked preponderance of nucleated red blood corpuscles (normoblasts) with a corresponding reduction in proportion of the cells of the granulocytic series.

24. Hemosiderosis is a deposition of hemosiderin resulting from the excessive destruction of erythrocytes.

TABLE 3.—*Miscellaneous Group of Blood Dyscrasias*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
				Hemolytic Anemia			
12	43 M	3 yr.	Exfoliative dermatitis	Palpable nodes	RBC, 2.4; hgb., 60%; WBC, 28,000; eosinophiles, 8%; marked anisocytosis, poikilocytosis, stippling, 1 normoblast per 100 WBC	Hyperplastic marrow and hemosiderosis	No improvement after splenectomy; cause of death: gastrointestinal hemorrhage*
13	37 F	8 yr.	Icteroid pallor; leg ulcer	Not palpable	RBC, 2.3; hgb., 46%; WBC, 5,400; differential count, normal; marked anisocytosis, poikilocytosis, achromia and occasional target cell	Erythroblastic hyperplasia and hemosiderosis	Splenomegaly, transfused at intervals
				Thrombocytopenic Purpura			
14	55 M	3 yr.	Showers of petechiae; large ecchymoses; reaction to tourniquet test positive	Not enlarged	RBC, 5.9; hgb., 104%; WBC, 12,150; differential count, normal; thrombocytes, 50,000-145,000; bleeding time, 5 min.; clot retraction incomplete after 24 hr.	Hyperplastic marrow with moderately abundant megakaryocytes	Causation undetermined; herpes zoster subsequently; no change in hemogram after 3 yr.
				Chronic Leucopenia			
15	41 M	2 yr.	Papulovesicular lesions on cheeks and shoulders	Not enlarged	RBC, 4.4; hgb., 90%; WBC, 2,000-3,900; polymorphonuclear leucocytes, 39-48%; lymphocytes, 48-55%; no abnormal cells	No significant change	Causation undetermined
16	64 F	4 yr.	Generalized pruritus	Palpable	RBC, 4.3; hgb., 80%; WBC, 2,800-3,800; polymorphonuclear leucocytes, 40-48%; lymphocytes, 49-58%; no abnormal cells	No significant change	Clinical and hematologic improvement following course of crude liver extract
				Polycythemia Vera			
17	73 M	?	Cyanosis and bullous polycythemia ?	Palpable	RBC, 7.8; hgb., 150%; WBC, 10,300; differential count, normal	Erythroblastic hyperplasia	Hepatomegaly and splenomegaly; autopsy: erythremia and portal cirrhosis of the liver
18	67 M	2 yr.	Cyanosis, acute urticarias and Bowen's disease of finger	Not enlarged	RBC, 7.5; hgb., 130%; WBC, 8,900; differential count, shift to left	Moderately cellular marrow, some admixture of blood	.....

* Dr. George Miller MacKee gave permission to include this case, and Mount Sinai Hospital, New York, supplied the final report.

TABLE 4.—*Lymphosarcoma*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
19	44 M	5 yr.	Serpiginous infiltrated plaques and 4 lentil-sized satellite lesions; histology: reticulum-cell sarcoma	Palpable	Normal	Slight increase in myelocytes and eosinophiles	Radiosensitive
20	50 M	6 mo.	Many nodules and plaques; histology: reticulum-cell sarcoma	Not palpable	Normal	No significant change	Autopsy*: reticulum-cell sarcoma
21	53 M	6½ yr.	Plaques and tumefaction; 2 biopsies: 1st, lymphoblastoma 2d, reticulum-cell sarcoma	Not palpable	Mild normocytic anemia	Slight increase in granulocytes and corresponding reduction in RBC	.....
22	73 M	18 mo.	Nodules and plaques; histology: lymphoblastoma	Not palpable	Normal	No significant change	Autopsy†: lymphosarcoma (mixed type)

* Memorial Hospital, New York, supplied this report.
† Bellevue Hospital, New York, supplied this report.

TABLE 5.—*Malignant Lymphogranuloma (Hodgkin's Disease)*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
23	38 M	6 mo.	Nodular infiltrations	Enlarged; histology: probable Hodgkin's disease	RBC, 3.5; hgb., 59%; relative polymorphonuclear leucocytosis	Increase in myelocytes and reduction in normoblasts	Died of Hodgkin's disease 1 yr. later
24	38 F	6 yr.	Pruritus, nodules and plaques; multiple ulcerations	Enlarged; histology: probable Hodgkin's disease	RBC, 3.9; hgb., 60%; WBC, 14,000; polymorphonuclear leucocytes, av. 83%	1st: no significant change	
		7 yr.	Eruptions more extensive		RBC, 2.9; hgb., 45%; WBC, 12,500; polymorphonuclear leucocytes, av. 84%	2d: granulocytic hyperplasia	Died of Hodgkin's disease 1 yr. later
25	52 M	5 yr.	Nodular infiltrations; histology: Hodgkin's disease	Enlarged; histology: Hodgkin's disease	Normal	No significant change	.....
26	35 M	2 yr.	Pruritus; diffuse and nodular infiltrations	Enlarged; histology: Hodgkin's disease	RBC, 4.0; hgb., 82%; WBC, 8,100; eosinophiles, 27%; monocytes, 14%	Granulocytic and eosinophilic hyperplasia	.....
27	72 F	13 mo.	Generalized pruritus and eczematization	Enlarged; histology: dermatopathic lymphadenitis	RBC, 4.2; hgb., 72%; WBC, 7,550; eosinophiles, 19%	Eosinophilic hyperplasia	Autopsy*: Hodgkin's disease

* Bellevue Hospital, New York, supplied this report.

plastic and megakaryocytes in moderate abundance were seen. No significant change was apparent in either of the cases of chronic leucopenia of undetermined origin.

Lymphosarcoma (Table 4).—Specimens from four cases of lymphosarcoma were examined. Three of the four lymphosarcomata were of the reticulum-cell type, and one was of the mixed-cell type. No abnormalities were seen in the marrow in two cases, and in two others the changes were of a nonspecific character—a slight increase in myelocytes and eosinophiles in one case and a slight increase in the mature leucocytes in the other.

Malignant Lymphogranuloma; Hodgkin's Disease (Table 5).—A total of six aspirations was performed in five cases of Hodgkin's disease. A hyperplasia of the neutrophilic and/or of the eosinophilic cells of the granulocytic series was observed in four of six specimens, and no significant change was noted in two aspirations. Neither megakaryocytic hyperplasia nor hyperplasia of the reticulum cells was apparent in any of the samples.

Mycosis Fungoides; Granuloma Fungoides (Table 6).—A total of 11 aspirations were performed in 10 cases of mycosis fungoides. In 5 of 11 aspirations there was no significant deviation from the normal, and in 6 of 11 specimens the changes were of a nonspecific nature. Granulocytic hyperplasia was noted in three specimens; eosinophilic hyperplasia, in one, and an eosinophilic hyperplasia with some increase in the plasma cells, in two specimens. There was no evidence of a *histioide* (reticuloendothelial) reaction in any aspirate.

Follicular Lymphoblastoma; Brill-Symmers Disease (Table 7).—No significant change was noted in the marrow.

Lymphoblastoma, Type Undetermined (Table 8).—A diagnosis of lymphoblastoma, type undetermined was made in 13 cases (39 to 51) since the clinical and laboratory observations were not specific for any entity belonging to the malignant lymphoma or lymphoblastoma group of diseases, e. g., lymphosarcoma, malignant lymphogranuloma (Hodgkin's disease), or mycosis fungoides. In two of the cases (50 and 51) no other designation was possible despite a postmortem examination. Among those (nine cases) in which the pathologic process appeared to be limited to the skin, an erroneous diagnosis might have been made in one or two instances (Cases 44 and 46). This possibility was entertained, since, as is well known, even on the basis of both the histologic and the clinical findings in the skin, the diagnosis of "cutaneous lymphoblastoma" often cannot be made with certainty.

A total of 16 aspirations was performed in 13 cases of lymphoblastoma, type undetermined. A diagnostic change was noted in the marrow in one case (42). In the other cases the marrow disclosed no significant change in 9 of 16 aspirations, a granulocytic hyperplasia in 2 of 16, an eosinophilic hyperplasia in 2 of 16, a slight increase in eosinophiles and plasma cells in 1 of 16, and some increase in plasma cells and some abnormal lymphoid forms in 1 of 16.

The clinical features in Case 42 were not distinctive. The patient had been ill for one year when he first was examined in our outpatient clinic. The macular erythematous eruption was seen over the face, neck, chest, shoulders, back, and upper extremities. The lesions were discrete, varying from the size of a dime to that of a quarter. Within 10 days the individual macules became somewhat ele-

TABLE 6.—*Mycosis Fungoides (Granuloma Fungoides)*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
28	50 F	4 yr.	Premycotic and infiltrative	Palpable	Normal	No significant change	Condition unchanged 2 yr. later
29	46 M	4 yr.	Infiltrative; leonine facies; exudative areas	Enlarged; histology: dermatopathic lymphadenitis	RBC, 4.0; hgb., 60%; WBC, 15,000; polymorphonuclear leucocytes, 72%; eosinophiles, 16%	Granulocytic hyperplasia	Autopsy: mycosis fungoides
30	40 F	4 yr.	Premycotic and infiltrative	Enlarged	RBC, 2.0; hgb., 44%; WBC, 19,000-40,000; eosinophiles, 8-44%	Eosinophilic hyperplasia	.....
31	58 M	10 yr.	Infiltrative and tumor	Palpable	Normal	No significant change	.....
32	76 M	12 yr.	Infiltrative	Small discrete glands	RBC, 4.2; hgb., 71%; eosinophiles, 2-23%; monocytes, 4-19%	Eosinophilic hyperplasia (slight); some increase in plasma cells	Cause of death: intestinal obstruction and cardiac failure
33	61 F	1 yr.	Erythroderma	Enlarged; histology: dermatopathic lymphadenitis	RBC, 4.1; hgb., 78%; WBC, 6,000-16,000; monocytes, 5-20%; lymphocytes, 14-70%	No significant change	Died 17 mo. later; cause of death not ascertained
34	29 M	6 yr.	Erythroderma and infiltrative	Enlarged; histology: dermatopathic lymphadenitis	RBC, 4.9; hgb., 75%; WBC, 3,500-5,500; eosinophiles, 10-14%	1st: granulocytic hyperplasia 2d: granulocytic hyperplasia with alteration of the myeloid/erythroid ratio	Died 6 mo. later; no autopsy
35	66 M	2½ yr.	Premycotic and infiltrative	Enlarged; histology: dermatopathic lymphadenitis	RBC, 3.6; hgb., 60%; WBC, 8,200-14,900; eosinophiles, 30-50%	Eosinophilic hyperplasia (slight) and plasma cells increased	Died 4 mo. later; no autopsy
36	68 M	1 yr.	Infiltrative	Enlarged	RBC, 3.4; hgb., 57%	No significant change	Autopsy*: mycosis fungoides
37	50 M	7 yr.	Tumor stage	Not enlarged	RBC, 3.8; hgb., 76%; WBC, 11,150-16,700	No significant change	No improvement with ACTH

* New York City Hospital, Welfare Island, New York, supplied this report.

TABLE 7.—*Follicular Lymphoblastoma*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
38	32 M	32 mo.	Papulovesicular eruption	Enlarged; histology: malignant lymphoma (giant follicular type)	Normal	No significant change	.....

TABLE 8.—*"Lymphoblastoma, Type Undetermined"*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
39	49 M	9 yr.	Clinical diagnosis: parapsoriasis en plaques; histology: lymphoblastoma (possible mycosis fungoides)	Not enlarged	Normal	Granulocytic hyperplasia and increase in myeloid/erythroid ratio	.....
40	27 M	7 mo.	Clinical diagnosis: exudative chronic discoid and lichenoid dermatitis ?; histology: lymphoblastoma (?)	Enlarged; histology: dermatopathic lymphadenitis	Eosinophilia (20%)	No significant change	Condition unchanged 4 yr. later
		4½ yr.	Clinical diagnosis: mycosis fungoides (?); histology: psoriasiform dermatitis with some changes suggestive of mycosis fungoides	Enlarged	Eosinophilia (10%)	Eosinophilic hyperplasia	
41	35 M	6 mo.	Clinical diagnosis: premycotic stage of mycosis fungoides; histology: lymphoblastoma	Not enlarged	Normal	No significant change	Radioresistant; presented by Dr. H. B. Van Dyke at New York Academy of Medicine, 4/7/42
42	58 M	1 yr.	Clinical diagnosis: lymphoblastoma; histology: lymphoblastoma	No enlargement except inguinal chain	Normal except for transitory relative eosinophilia (8%) and monocytosis (11%)	Lymphoid infiltration	Diagnosis of chronic lymphatic leukemia made at Kings County Hospital*
43	54 M	3 yr.	Clinical and histologic diagnosis: lymphoblastoma	Palpable cervical and inguinal nodes; no enlargement of mediastinal nodes	Normal	No significant change	Radioresistant; general condition good; skin and general condition unchanged 2 yr. later
44	43 F	7 wk.	Clinical diagnosis: lymphoblastoma; histology: lymphoblastoma (Spiegler-Fendt [?])	Not palpable	5 blood counts within normal limits; on one occasion: WBC, 6,400; lymphocytes, 60%; occasional atypical lymphocyte	No significant change	Radiosensitive; healed after 1,200 r (unfiltered)
45	39 F	5 yr.	Clinical diagnosis: neurodermatitis (?); lymphoblastoma ?; histology: mycosis fungoides	Not palpable	Normal	No significant change	Histology (4 mo. later): nonspecific dermatitis†
46	61 M	3 yr.	Clinical diagnosis: neurodermatitis ?; histology: malignant lymphoma, leukemia cutis (?)	Shotty enlargement	Normal	No significant change	Definitely improved 6 mo. later
47	31 F	1 yr.	Clinical diagnosis: mycosis fungoides (?), parapsoriasis en plaques (?); histology: mycosis fungoides (?)	Not palpable	Normal	Slight increase in eosinophiles and plasma cells	Eruption progressively more widespread; 3 histologic examinations during the next 3 yr. were interpreted as lymphoblastoma (?); lymphoblastoma, mycosis fungoides (?), and mycosis fungoides (?)
48	60 M	4½ yr.	Clinical diagnosis: psoriasiform dermatitis; 2 histologic sections: 1st: early mycosis fungoides ?, toxic dermatitis ? 2d: histology unchanged	Palpable	Normal	Slight increase in plasma cells and some abnormal lymphoid cells	Clinical picture unchanged 5 yr. later

49	74 M	1 yr.	Clinical and histologic diagnosis on admission and 6 mo. later: lymphoblastoma	No enlargement of superficial or mediastinal nodes	RBC, 3.5; hgb., 54%; achromia and poikilocytosis	1st: no significant change 2d: granulocytic hyperplasia; increase in the myeloid/erythroid ratio	Died 4 mo. after 2d aspiration; autopsy: acute aleukemic leukemia (monocytic [?])‡
50	28 F	3 yr.	Multiple ulcerations and plaques; clinical diagnosis: lymphoblastoma; histology: (*a*) ulcer, granulation tissue (*b*) plaques, lymphosarcoma (?)	No enlargement of superficial or mediastinal nodes	Progressive anemia; WBC, 10,000-23,000; eosinophiles, 22-57%	Eosinophilic hyperplasia	Autopsy: malignant lymphoma, type undetermined
51	66 M	2 yr.	Clinical diagnosis: dermatitis; histology (2 sites): mycosis fungoides	Enlarged	RBC, 3.5; hgb., 68%; WBC, 6,000-21,750; lymphocytes, av. 78%; occasional atypical lymphocyte	Cellular marrow; no abnormal forms	
		3 yr.	Clinical diagnosis: leukemia cutis; histology: leukemia cutis	Enlarged; histology: lymphatic leukemia of epitrochlear node	Essentially the same	No significant change	Autopsy: mycosis fungoides (?) with lymphosarcoma terminally (?)§

* Kings County Hospital, Brooklyn, supplied this report.
† Presbyterian Hospital (Columbia-Presbyterian Medical Center) New York, supplied this report.
‡ Kings County Hospital, Brooklyn, supplied this report.
§ Dr. David A. Karnofsky and Memorial Hospital, New York, permitted us to use this report.

vated and smooth to the touch. No scaling was evident, nor did the patient complain of any itching. The eruption proved to be radiosensitive. As the treated lesions resolved, new lesions appeared on the right buttock, left mandibular area, and the occiput. These plaques were more infiltrated than the earlier lesions. No enlargement of the lymph nodes was noted except in the inguinal chain. The edge of the liver was palpable on deep inspiration, but the splenic border could not be felt. Repeated blood counts were normal, except for a relative monocytosis (the monocytes varying from 8 to 11% of the differential count) and a relative eosinophilia (the eosinophile count varying from 8 to 11%) in three of five examinations.

Histologic examination of the skin disclosed rather large, fairly well-defined cellular masses throughout the corium. These masses were composed of lymphocytes which varied in size and shape and contained nuclei with a hyperchromatic intranuclear network and one or more nucleoli. Scattered mitoses were also seen. A histologic diagnosis of lymphoblastoma was entertained.

The striking feature of the marrow was the presence of a considerable proportion of primitive nongranular cells which were considered to be the precursors of either myeloid or lymphoid cells. These blasts had a basophilic cytoplasm, often scanty, the nucleus sometimes filling the cells. Occasionally, the nucleus was lobulated. No granules were seen in the cytoplasm, even in those cells in which the cytoplasm was abundant. A number of megakaryocytes was present, associated with clumped thrombocytes (platelets). There was no apparent deviation in the development of the erythrocytes or the granular leucocytes.

It was difficult to state from the observations on the marrow alone whether the infiltrate was leukemic or metastatic, or whether the cells were myeloblasts or lymphoblasts. A presumptive diagnosis of lymphoid infiltration of the marrow was made in view of the character of the infiltrate in the cutis.

Two months later a diagnosis of chronic lymphatic leukemia was made by physicians at the Kings County Hospital, Brooklyn. The hemogram obtained at that hospital read as follows.[25]

Leucocytes	10,000 per cu. mm.
Segmented polymorphonuclear neutrophiles	33%
Segmented polymorphonuclear basophiles	3%
Segmented polymorphonuclear eosinophiles	4%
Lymphocytes	44%
Monocytes	15%
Plasma cells	1%
Disintegrated cells	13%

Idiopathic Hemorrhagic Sarcoma; Kaposi's Sarcoma (Table 9).—The cases selected for study were typical. Five aspirations were made in as many cases. There was no significant change in two; a slight eosinophilic hyperplasia was present in the third and a granulocytic hyperplasia in the fourth. In the fifth case there was sufficient admixture of blood to invalidate the results.

Sarcoidosis (Table 10).—Four cases were selected. In three of four there was evidence of systemic involvement (Schaumann's disease), and in one the process appeared to be limited to the skin. One of the patients (Case 60) had sickle-cell anemia as well.

25. Kings County Hospital, Brooklyn, supplied this report.

TABLE 9.—*Idiopathic Hemorrhagic Sarcoma (Kaposi's Sarcoma)*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
52	67 M	7 yr.	Clinical diagnosis confirmed by histologic examination	Not palpable	Normal	No significant change	2 yr. later developed an infiltrating adenocarcinoma of rectosigmoid with lymph node metastases; 4 yr. later diagnosis of idiopathic hemorrhagic sarcoma reaffirmed
53	42 M	4 yr.	Typical	Not palpable	Eosinophiles, 9%	Slight eosinophilic hyperplasia	.....
54	40 F	8 yr.	Typical	Not palpable	RBC, 3.8; hgb., 74%	Granulocytic hyperplasia	.....
55	65 M	9 mo.	Typical	Not palpable	Relative monocytosis (9-18%)	No significant change	.....
56	52 M	4 yr.	Typical, confirmed by histologic examination	Not palpable	Normal	Admixed with blood	.....

TABLE 10.—*Sarcoidosis*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
57	25 F	1 yr.	Extensive eruption; histology: sarcoidosis	Palpable	RBC, 4.4; hgb., 68%; WBC, av. 3,100; lymphocytes, av. 20%; monocytes, av. 12%	Sarcoidosis	Splenomegaly; hepatomegaly
58	42 M	1 yr.	Macular eruption; histology: sarcoidosis	Not palpable	RBC, 5.4-6.2; hgb., 112-116%; differential count, normal	Cellular marrow; lymphocytes in upper limits of normal range; occasional vacuolated monocyte	No roentgenographic signs of pulmonary infiltration
59	42 F	4 yr.	Extensive macular and nodular eruption; histology: sarcoidosis	Epitrochlear and inguinal nodes enlarged	RBC, 4.1; hgb., 62%	No significant change	Hepatomegaly; splenomegaly; extensive infiltration of mid-lung fields
60	38 F	1 yr.	Extensive eruption; histology: sarcoidosis	Enlarged; histology: sarcoidosis	Sickle-cell anemia	Marked erythroblastic hyperplasia secondary to sickle-cell disease	Autopsy: disseminated sarcoidosis; marrow, usual type cells and in usual proportions

Sarcoidosis of the marrow was found in one of four cases (Case 57). The marrow in this case was sectioned. Smears, regrettably, were not made for comparison. The sections showed a moderately cellular marrow in which two granulomas were observed. These were made up of spheroidal aggregations of epithelioid cells showing no necrosis and no giant cells. One was quite naked, and the other was surrounded by a thin cuff of lymphoid cells. The specimens otherwise showed the usual proportion of white and red blood cells, without disturbance in maturation. The marrow disclosed no notable change in one case, an occasional vacuolated lymphocyte with the lymphocytes in the upper limits of the normal range in one case, and a secondary erythroblastic hyperplasia in the case of sickle-cell anemia.

Exfoliative Dermatitis (Table 11).—Chronicity, obscure pathogenesis, and the lack of histopathologic changes which were diagnostic of any particular dermatologic entity (e. g., psoriasis) were the criteria used in the selection of the cases designated as exfoliative dermatitis.

The most noteworthy change in the exfoliative erythrodermas was an eosinophilic hyperplasia of the marrow. This reaction was noted in 5 of 11 cases. A slight increase in the number of eosinophiles, insufficient to be designated a hyperplasia, was seen in an additional case. In two of the specimens, the eosinophilic hyperplasia was combined with a granulocytic hyperplasia. The other case in this category showed a granulocytic hyperplasia without an increase in the eosinophiles in two instances, a moderate increase in plasma cells in one, and no noteworthy change in two cases. An eosinophilia in the peripheral blood was present in all cases with eosinophilia in the marrow.

Eczematous and Eczematoid Eruptions (Table 12).—Only those cases of eczema or eczematoid eruptions that were extensive or generalized, and of a chronic or recurrent nature, were considered suitable for study. Diverse conditions, e. g., psoriasiform eczema, neurodermatitis, and distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger-Garbe syndrome), were included. An eosinophilic hyperplasia of the marrow was found in five of seven cases; no significant change, in one, and marrow admixed with blood, in one. An elevated eosinophile count in the circulating blood was observed in each of the cases associated with an eosinophilic hyperplasia of the marrow.

Miscellaneous Group of Dermatoses (Table 13).—Diagnostic changes in the marrow were not revealed in any of the cases included in this group. Replacement of one portion of the marrow by tumor cells, however, was seen on postmortem examination in the case of hemangioendothelioma of the skin.[26]

The failure to find the L.E. cell in the marrow in the case of acute lupus erythematosus disseminatus (Case 79) may be attributed to the fact that direct smears, rather than heparinized centrifuged marrow, were used. Regrettably, we were not familiar with the technique advocated by Hargraves[27] when the examination was made.

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26. This case was reported in detail by A. I. Weidman (Hemangioendothelioma of the Skin with Metastases to Liver, Lungs and Lymph Nodes, Arch. Dermat. & Syph. **62**:655-661, 1950).

27. Hargraves, M. M.: Production in Vitro of the L. E. Cell Phenomenon: Use of Normal Bone Marrow Elements and Blood Plasma from Patients with Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **24**:234-237, 1949.

TABLE 11.—*Exfoliative Dermatitis*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
61	59 M	18 mo.	Histology: superficial inflammatory process	Enlarged; histology: dermatopathic lymphadenitis	Normal	No significant change	Pleural exudate in lower 4th of left pulmonary field
62	66 M	2 yr.	Histology: 2 sections: 1st: mycosis fungoides (?) 2d: psoriasis (?)	Palpable	Relative monocytosis (12%)	Slight granulocytic hyperplasia	Recovered
63	60 M	6 mo.	Histology: 2 sections: 1st: lymphoblastoma ? 2d: psoriasis	Enlarged; histology: dermatopathic lymphadenitis	RBC, 4.6; hgb., 74%; WBC, 14,800-15,450; eosinophiles, 16-28%	Mild eosinophilic hyperplasia	.....
64	65 M	3 yr.	Histology: 2 sections: 1st: chronic dermatitis ?; lymphoblastoma ? 3d: no change 1 mo. later	Enlarged; histology: dermatopathic lymphadenitis	WBC, 5,000-11,100; eosinophiles, 4-22%; monocytes, 2-15%	1st: admixed with blood 2d: slight eosinophilic and granulocytic hyperplasia	Progressively worse while under observation
65	58 M	6 mo.	Histology: probable lymphoblastoma	Enlarged; histology: dermatopathic lymphadenitis	WBC, 5,000-9,100; eosinophiles, 1-9%; monocytes, 5-15%	Slight increase in eosinophiles and plasma cells	Autopsy: exfoliative dermatitis; uremia secondary to hemorrhagic nephritis
66	64 M	8 yr.	Histology: lymphoblastoma	Shotty nodes	RBC, 4.0; hgb., 75%; WBC, 5,100-8,950; eosinophiles, 2-8%	No significant change	Unchanged 2 yr. later
67	47 M	4 mo.	Histology: chronic eczema; lymphoblastoma (?)	Enlarged; histology: dermatopathic lymphadenitis	WBC, 9,000-21,000; eosinophiles, 5-18%; monocytes, 5-12%; occasional atypical lymphocytes	Slight eosinophilic hyperplasia	Died 2 yr. later of a gastrointestinal hemorrhage
68	44 F	7 mo.	Histology: chronic eczema	Shotty enlargement	Progressive anemia; RBC, 3.5; hgb., 68%; WBC, 9,800-13,100; eosinophiles, 15-24%	Slight eosinophilic hyperplasia	Unchanged 1 mo. later
69	52 F	3 yr.	Histology: lymphoblastoma; possible mycosis fungoides ?	Enlarged; histology: dermatopathic lymphadenitis	WBC, 8,650-14,300; lymphocytes, 46-77%; occasional atypical lymphocytes	Cellular marrow with increase in erythroid/myeloid ratio	Gradual improvement over 2-yr. period
70	55 F	2 yr.	Histology: lymphoblastoma ?	Enlarged; histology: dermatopathic lymphadenitis	RBC, 3.7; hgb., 62%; occasional atypical lymphocytes	Moderate increase in plasma cells	Unchanged 1 mo. later
71*	74 M	1 yr.	Histology: lymphoblastoma	Enlarged; histology: dermatopathic lymphadenitis	RBC, 3.1; hgb., 65%; WBC, 11,850-23,850; eosinophiles, 3-28%	Granulocytic and eosinophilic hyperplasia; lymph follicles noted	Unchanged 3 mo. later

* Dr. John Garb gave permission for inclusion of this case.

TABLE 12.—*Eczematous and Eczematoid Eruptions*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
72	72 M	7 mo.	Clinical diagnosis: eczema; histology: 1st: contact dermatitis (?) 2d: lymphoblastoma ?	Palpable	RBC, 5.1; hgb., 73%	No significant change	Healed a few mo. later
73	51 M	9 mo.	Clinical diagnosis: neurodermatitis; histology: suggests exudative discoid and lichenoid dermatitis	Palpable	WBC, 25,000-28,500; eosinophiles, 5-9%	Eosinophilic hyperplasia	Responded well to hospitalization
74	39 M	18 mo.	Clinical diagnosis: atopic dermatitis ?; histology: suggests exudative discoid and lichenoid dermatitis	Palpable	RBC, 4.6; hgb., 75%; WBC, 10,900-14,800; eosinophiles, 15-24%	Eosinophilic hyperplasia	Lived in El Paso, Texas, for 5 yr.; decided improvement with change of environment
75	60 M	2 mo.	Clinical diagnosis: eczema; histology: suggests exudative discoid and lichenoid dermatitis	Enlarged; histology: dermatopathic lymphadenitis	WBC, 11,500; eosinophiles, 27%	Eosinophilic hyperplasia	Improved while in the hospital
76	47 M	Few mo.	Clinical diagnosis: eczema; histology: suggests exudative discoid and lichenoid dermatitis	Not enlarged	WBC, 12,900-16,450; eosinophiles, 9-18%	Eosinophilic hyperplasia	.....
77	74 M	6 yr.	Clinical diagnosis: eczema; histology: neurodermatitis	Enlarged	RBC, 3.5; hgb., 64%	Considerable admixture of blood	.....
78	57 M	2 yr.	Psoriasiform eruption; histology: changes compatible with lymphoblastoma	No enlargement of superficial or mediastinal nodes	WBC, 6,200-8,900; eosinophiles, 7-8%	Mild eosinophilic hyperplasia	Recovered; final diagnosis: contact dermatitis

TABLE 13.—*Miscellaneous Group of Dermatoses*

Case No.	Age; Sex	Duration	Skin	Lymph Nodes	Hemogram	Myelogram	Comment
				Acute Lupus Erythematosus Disseminatus			
79	12 F	7 mo.	Typical "butterfly" distribution, palms involved	Axillary nodes palpable	RBC, 3.3-2.1; WBC, 2,500-4,200; atypical lymphocytes and polymorphonuclear cells	1st: slight granulocytic hyperplasia, no L. E. cells (direct smear) 2d: increased number of reticulum cells, no L. E. cells (direct smear)	Pericardial effusion; hepatomegaly; splenomegaly; autopsy: lupus erythematosus disseminatus
				Subacute Lupus Erythematosus Disseminatus			
80	47 F	3 mo.	Lesions on face, forearms and hands	Not palpable	RBC, 3.7; hgb., 80%; monocytosis (17%) on 1 count	Slight granulocytic hyperplasia of bone marrow; no L. E. cells found on direct smear	.....
81	24 F	4 yr.	Lesions on face and hands	Not palpable	RBC, 3.8; hgb., 74%; WBC, 2,000-3,200; differential count, normal limits	Heparinized marrow: cellular, usual variety of nucleated forms, no L. E. cells	L. E. phenomenon negative; no L. E. cells found in peripheral blood
				Chronic Discoid Lupus Erythematosus			
82	55 M	5 mo.	Histology: lupus erythematosus	Not palpable	Relative monocytosis (12-14%) present consistently	Some admixture with blood; no abnormal cells; no L. E. cells found on direct smear	.....
				Lichen Planus			
83	58 M	..	Histology: lichen planus	Not palpable	WBC, 3,000-5,500; eosinophiles, 3%	Eosinophilic and granulocytic hyperplasia	Leucopenia followed bismuth administration parenterally; 16 injections of crude liver extract administered prior to sternal puncture
				Malignant Hemangioendothelioma			
84	71 F	7 mo.	Scalp tumor, diffuse erythema, and edema of head and neck	"Tumor-like" swellings of cervical nodes	Eosinophilia (5-18%)	No tumor cells	Autopsy: primary malignant hemangioendothelioma of skin and subcutis, 1 portion of bone marrow replaced by tumor cells

A granulocytic (principally myelocytic) and an eosinophilic hyperplasia was found in the cases of lichen planus. The aspiration was made after the patient had received crude liver extract combined with bismuth therapy. At the time of the sternal aspiration the hemogram showed 3,000 white blood cells per cu. mm. and a relative lymphocytosis. The eosinophiles comprised 3% of the differential count. The eosinophile count remained within a normal limit on subsequent examinations. There appeared to be no correlation between the myelogram and the hemogram in this instance.

COMMENT

Our observations on the various entities studied are compared and contrasted with those of earlier observers. Chronic lymphatic leukemia, lymphosarcoma (including reticulum-cell sarcoma of lymph nodes), Hodgkin's disease, follicular lymphoblastoma, and mycosis fungoides are discussed under separate headings, although many observers prefer to treat these conditions as a group (malignant lymphomas).

Leukemia.—The hematologic observations, together with the clinical features, enabled us to make a definitive diagnosis of chronic lymphatic leukemia in five of eight cases. The observation of lymphoid infiltration in the marrow in four of these cases (1, 4, 6, and 8) served to confirm the clinical diagnosis. The failure to demonstrate lymphoid infiltration in the marrow in Case 7, on the other hand, did not exclude the diagnosis of chronic lymphatic leukemia, for it has been shown conclusively [2b] that normal marrow may be aspirated in this blood dyscrasia because the involvement may be patchy rather than diffuse.

The paucity of the clinical findings and the absence of a characteristic hemogram left the diagnosis in doubt in three cases. The demonstration of lymphoid infiltration in the marrow in Case 5 and the presence of lymphoid infiltration in the nodes and in the marrow in Cases 2 and 3 served to establish the diagnosis. Sternal aspiration was particularly valuable from the diagnostic viewpoint in Case 5, since excision of one of the lymph nodes for histologic examination was not feasible, in view of their small size. Our experience was in accord with that of Welch,[6a] who maintained that marrow studies were "of the utmost value in the diagnosis of chronic lymphatic leukemia, because atypical forms [of the disease] are quite common."

The monocytic and myelocytic infiltrate in the marrow in the case of monocytic leukemia (Naegeli type) mirrored the changes in the peripheral blood. Examination of the marrow in Case 49, a questionable case of acute monocytic leukemia, failed to disclose diagnostic changes. Hubler and Netherton [6b] showed that initial bone marrow studies were diagnostic in 15 of 20 of their cases of Schilling type of monocytic leukemia associated with cutaneous manifestations. They were of the opinion that studies of the bone marrow were of considerable diagnostic value in the latter blood dyscrasia, since days or weeks might elapse before diagnostic immature monocytes appeared in the peripheral blood.

Chronic Lymphatic Leukemia or Lympholeukemoid Reaction.—The inability to demonstrate lymphoid infiltration either in the bone marrow or in the lymph nodes in Cases 10 and 11 (repeated examinations were made in Case 11) left the differential diagnosis in doubt. Whereas a positive demonstration either in the marrow

or in the lymph node would have served to establish the diagnosis of leukemia, the negative observations did not exclude the possibility. These cases brought to mind a report by Fraser [28] on "Exfoliative Dermatitis with a Leukemoid Blood Picture." Fraser's patient, however, made an uneventful recovery.

Miscellaneous Group of Blood Dyscrasias.—Our observations in this group are in agreement with those previously reported in hemolytic anemia,[29] thrombocytopenic purpura,[30] and polycythemia vera.[2b] The absence of diagnostic changes in the marrow in the cases of unexplained chronic leukopenia left the pathogenesis of the leucopenia in doubt. Nevertheless, sternal aspiration is a valuable diagnostic aid in the study of leucopenia and agranulocytosis of obscure origin.[31]

The possible association of chronic or recurrent leg ulcers with sickle-cell anemia and congenital hemolytic icterus is generally known. The concurrence of leg ulcers with hereditary leptocytosis, however, was not recognized until recently.[32] The case included in this report is probably among the first to appear in the dermatologic literature.

Lymphosarcoma.—Our results may be compared only with those previously obtained in studies on the reticulum-cell or mixed-cell type of lymphosarcoma. The studies [33] in which the type of lymphosarcoma has not been designated or those dealing with the lymphatic form of the diseases are not entirely pertinent. Limarzi and Paul [34] did not observe any abnormalities in the marrow, except for a hyperplasia in five cases of reticulum-cell sarcoma. This coincides with our experience in four cases. Rohr and Hegglin,[35] on the other hand, reported unusually large undifferentiated cells in one case of reticulum-cell sarcoma. The technique employed in preparing the marrow may prove to be of considerable importance in determining the results to be obtained with this diagnostic tool. Cooper and Watkins [7a] found that sternal aspiration was of decided value in differentiating lymphosarcoma from other forms of malignant lymphoma when fixed section preparations were used rather than smears. Custer [2b] was able to demonstrate infiltration of the marrow with reticulum cells in a case of reticulum-cell (Hodgkin's) sarcoma in which fixed sections had been made.

Malignant Lymphogranuloma (Hodgkin's Disease).—A hyperplasia of the neutrophilic and the eosinophilic cells of the myeloid series was observed in four of six specimens obtained in Hodgkin's disease. Earlier reports have described essen-

28. Fraser, J. F.: Exfoliative Dermatitis with a Leukemoid Blood Picture Indistinguishable from Lymphatic Leukemia, Arch. Dermat. & Syph. **48**:42-46, 1943.

29. Case, R. A. M.: Siderocytes in Hemolytic Diseases: A New Index of Severity and Progress, J. Path. & Bact. **57**:271-273, 1945.

30. Diggs, L. W., and Hewlitt, J. S.: A Study of the Bone Marrow from 36 Patients with Idiopathic Hemorrhagic (Thrombopenic) Purpura, Blood **3**:1090-1104, 1948.

31. Vogel, P.; Erf, L. A., and Rosenthal, N.: Hematological Observations in Bone Marrow Obtained by Sternal Puncture, Am. J. Clin. Path. **7**:436, 498-515, 1937.

32. Estes, J. E.; Farber, E. M., and Stickney, J. M.: Ulcers of the Leg in Mediterranean Disease, Blood **3**:302-306, 1948.

33. Cooper and Watkins.[7a] Falconer, E. H., and Leonard, M. E.: The Value of Sternal Marrow Aspiration as a Method of Bone Marrow Biopsy, Ann. Int. Med. **15**:446-458, 1941.

34. Limarzi, L. R., and Paul, J. T.: Sternal Marrow Studies in Hodgkin's Disease, Am. J. Clin. Path. **19**:929-961, 1949.

35. Rohr, K., and Hegglin, R.: Tumorzellen im Sternalpunktat, Deutsches Arch. klin. Med. **179**:61-79, 1936.

tially the same changes except for an associated increase in the reticulum cells noted by a few observers. Limarzi and Paul [34] were of the opinion that moderate to extreme megakaryocytic hyperplasia associated with myeloid hyperplasia was one of the constant observations. The consensus is that there are no pathognomonic changes in the marrow in Hodgkin's disease [36] and that the demonstration of the Sternberg-Reed cell [37] is certainly the exception rather than the rule. Fixed sections of the marrow, as prepared by Cooper and Watkins,[7a] failed to reveal more than a distinct hyperplasia with myeloid preponderance in about half the specimens.

Mycosis Fungoides (Granuloma Fungoides).—Ten samples of marrow were obtained in nine cases of mycosis fungoides. In 4 of 10 specimens there was no significant deviation from the normal, and in 6 of 10 the changes were of a nonspecific nature. Granulocytic hyperplasia, eosinophilic hyperplasia, and some increase in plasma cells were noted. We failed to find the polymorphous *histioide* reaction described by Lapiere and de Weerdt,[16a] Santoianni,[16b] and Tzanck [16c] in some of their cases. Tilley and Smith [16d] and de Graciansky and Paraf [17] likewise failed to note either a reticuloendothelial reaction or histiocytes peculiar to mycosis fungoides.

Follicular Lymphoblastoma (Brill-Symmers Disease).—No essential change was apparent in the marrow in the case of follicular lymphoblastoma. Cooper and Watkins [7a] studied two cases. In one there was a slight increase in normal lymphocytes, and in the other, a myeloid hyperplasia. Wintrobe [38] also reported an increase in lymphocytes in one case of follicular lymphoma. No pathognomonic features have been reported to date.

Lymphoblastoma, Type Undetermined.—Lymphoid infiltration of the marrow was observed in 1 of 13 cases (1 of 16 aspirations), in a patient in whom the pathologic process otherwise appeared to be limited to the skin. This observation serves to call attention to the fact that a so-called cutaneous lymphoblastoma may not be regarded as being limited to the skin unless a thorough examination of the patient is made. The results, on the other hand, also make it clear that the pathologic process may be extensive, as in Cases 49, 50 and 51, without any demonstrable change in the marrow. Case 42 illustrates also that the marrow may be the seat of a lymphoid infiltrate when the hemogram is within normal limits or shows merely minor deviations from the normal. Wayson and Weidman [7b] likewise stressed the importance of studies of the peripheral blood and examination of the sternal marrow in cases of so-called cutaneous lymphoblastoma.

Idiopathic Hemorrhagic Sarcoma (Kaposi's Sarcoma).—The marrow in these cases showed either no notable change or nonspecific changes, e. g., eosinophilic and granulocytic hyperplasia. We failed to observe the *histioide* cells described by Bessone [15] in his report on three cases.

Sarcoidosis.—Epithelioid-cell granulomas appeared in the marrow in one of four cases; this case was one of generalized sarcoidosis. There were two other examples of generalized sarcoidosis in this group in which changes pathognomonic

36. Steiner,[7c] Campion, W. M., and Diggs, L. W.: Bone Marrow Studies in Hodgkin's Disease, Cleveland Clin. Quart. **15**:36-41, 1948. Morrison, M., and Samwick, A. A.: Clinico-Hematologic Evaluation of Bone Marrow Biopsies, Am. J. M. Sc. **198**:758-773, 1939.

37. Varadi, S.: L'infiltration lympho-granulomateuse du sternum: Sur un cas de maladie de Hodgkin diagnostiqué par ponction sternale, Sang **12**:106-110, 1938.

38. Wintrobe, M. M.: Clinical Hematology, Ed. 2, Philadelphia, Lea & Febiger, 1946, p. 734.

of the disease could not be demonstrated in the marrow. That typical granulomas are not disclosed in every case is shown by the results in other series as well as ours. Gormsen [8b] found typical granulomas in 10 of 39 cases. Leitner,[2a] on the other hand, did not find epithelioid tubercles in any of a group of 19 cases.

Exfoliative Dermatitis.—Examination of the marrow in 11 cases of exfoliative dermatitis of unknown causation failed to shed any light on the pathogenesis or cause of the disease. The most noteworthy change was a varying degree of hyperplasia of the eosinophiles, of both the myelocytic and the mature forms. The association of exfoliative dermatitis with a marrow and blood eosinophilia has been noted by others.[31] An eosinophilia in the blood was noted in each of the cases associated with an eosinophilic hyperplasia of the marrow.

Eczematous and Eczematoid Eruptions.—Sternal aspiration failed to disclose any diagnostic features in this group. The most consistent observation was an eosinophilic hyperplasia of varying degree. A corresponding increase in the number of eosinophiles in the circulating blood was noted in each of the cases associated with an eosinophilic hyperplasia.

Miscellaneous Group of Dermatoses.—The failure on two occasions to demonstrate the L.E. cell in the marrow in one case of acute lupus erythematosus disseminatus may have been due to faulty technique. However, it should be pointed out that L.E. cells are not always demonstrable in this disease. They were observed in 7 of 11 of Morton's cases,[39] in 4 of 5 of Haserick and Sundberg's cases,[40] in 5 of 7 of Montgomery and McCreight's patients,[41] and in 4 of 8 of Madden's cases.[42] The consensus is that the L.E. cell cannot be demonstrated in the marrow in the subacute or chronic forms of lupus erythematosus. We examined sections from one case of the subacute form, using the technique advocated by Hargraves,[27] and likewise failed to find the L.E. cell.

The eosinophilic hyperplasia of the marrow in a single case of lichen planus is attributable to the parenteral injection of crude liver extract administered prior to the aspiration.

Although metastases to the marrow have been demonstrated by sternal aspiration in diverse tumors,[43] they are not found with any degree of regularity. Nor did the absence of metastatic deposits in the sternal aspirate in the case of malignant hemangioendothelioma preclude their presence in other parts of the marrow.

In the cases selected, eosinophilic hyperplasia of the marrow was observed more frequently than any other nonspecific change in the myelogram. It was found in 5 of 7 cases of eczematous and eczematoid eruptions, in 5 of 12 cases of exfoliative dermatitis, in 2 of 5 cases of Hodgkin's disease with cutaneous involvement, in 3

39. Morton, R. J.: A Study of the Blood and Bone Marrow in Cases of Disseminated Lupus Erythematosus, Thesis, University of Minnesota, 1947.

40. Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus: Report on the Hargraves' "L. E." Cell, J. Invest. Dermat. **11**:209-213, 1948.

41. Montgomery, H., and McCreight, W. G.: Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. **60**:356-372, 1949.

42. Madden, J. F.: Comparison of Muscle Biopsies and Bone Marrow Examinations in Dermatomyositis and Lupus Erythematosus, Arch. Dermat. & Syph. **62**:192-205, 1950.

43. Footnote 2. Jonsson and Rundles.[3] Vogel and others.[31]

of 10 cases of mycosis fungoides, in 2 of 13 cases of lymphoblastoma, type undetermined, and in a single case of lichen planus. A correlation between marrow eosinophilia and blood eosinophilia was noted in all but two of the cases. The exceptions to the rule were Case 39 (lymphoblastoma, type undetermined) and Case 82 (lichen planus). In the former an eosinophilia (20%) in the peripheral blood was associated with a normal myelogram. In this case an eosinophilic hyperplasia of the marrow ultimately developed. In the latter case an eosinophilic hyperplasia of the marrow was associated with a normal number of eosinophiles in the peripheral blood.

Leitner [28] has discussed the correlation of blood and marrow eosinophilia in considerable detail. He maintained that in "allergic states" a marked marrow eosinophilia is invariably present when there is a blood eosinophilia and that an eosinophilia of the marrow may be present even though eosinophiles in the peripheral blood are normal or less than normal. The latter occurred in Case 82. In Case 39, we saw an example of blood eosinophilia without a demonstrable eosinophilia in the marrow. Although there appears to be a high degree of correlation between marrow and blood eosinophilia, the correlation is not invariably present, as shown in this study and in the reports of others.[31]

SUMMARY AND CONCLUSIONS

The sternal marrow findings are reported in 84 cases of selected dermatoses studied during the period 1942 to 1950. In these cases, a total of 95 aspirations was performed in order to ascertain the diagnostic value of this procedure in the study of dermatological conditions.

The procedure was of particular value in reaching a more accurate diagnosis of atypical cases of chronic lymphatic leukemia, associated with specific and nonspecific changes in the skin. That the need for such a diagnostic aid may arise not infrequently is shown by the large proportion of atypical cases (three of eight) that came to our attention.

Pathognomonic or diagnostic changes in the marrow were also seen in 1 of 4 cases of sarcoidosis; in a single case of monocytic leukemia (Naegeli type), and in 1 of 13 cases of "lymphoblastoma, type undetermined." The last observation illustrates the fact that the marrow may be the seat of a lymphoid infiltration when the lymphoblastoma otherwise appears to be limited to the skin.

Changes of a nonspecific character or essentially unaltered marrow were found in lymphosarcoma, follicular lymphoblastoma (Brill-Symmers disease), Hodgkin's disease, mycosis fungoides, idiopathic hemorrhagic sarcoma (Kaposi's sarcoma), exfoliative dermatitis, and the widespread eczematous and eczematoid eruptions of unknown causation. Eosinophilic hyperplasia was noted oftener than any other nonspecific change in the myelogram (18 of 84 cases).

A review of the literature shows that examination of the marrow is also of value in the diagnosis of malignant melanoma with metastases, acute lupus erythematosus disseminatus, and monocytic leukemia (Schilling type) with cutaneous involvement.

NOTE.—In view of the accidental deaths following sternal puncture that have been reported recently,[44] it is important to add that this procedure is not entirely an innocuous one.

44. Fortner, J. G., and Moss, E. S.: Death Following Sternal Puncture, Ann. Int. Med. **34**:809-815, 1951.

Dr. Charles F. Sims, Dr. Else Ann Barthel, and Dr. Charles S. Miller studied the biopsy specimens of the skin. Dr. Max Scheer, Dr. Nathan Sobel, Dr. Jesse A. Tolmach, and Dr. Jack Wolf permitted us to study the patients admitted to their respective services at the Skin and Cancer Unit, University Hospital of New York University-Bellevue Medical Center, New York.

ABSTRACT OF DISCUSSION

Dr. Edward P. Cawley, Charlottesville, Va.: As Dr. Pascher has pointed out, reports dealing with bone marrow studies in diseases which affect chiefly the skin are relatively few. Her results with the lymphoblastomata and blood dyscrasias are in general accord with those of other investigators. Dr. Pascher has found sternal marrow alterations to be especially valuable in establishing a correct diagnosis in atypical cases of chronic lymphatic leukemia associated with specific and nonspecific changes in the skin. This statement warrants all the emphasis she has given it, because many such cases are difficult diagnostic problems. The results of bone marrow examination in the cases of exfoliative dermatitis and eczematoid eruptions were instructive, even though diagnostic features were not found in the marrow in these disorders.

Dr. Pascher studied one case of hemangioendothelioma of the skin, but she did not find metastatic deposits in the sternal marrow. As she mentioned, however, the absence of such deposits in the sternal marrow did not preclude their presence in other parts of the marrow. Perhaps all of us might be wise to do marrow studies searching for evidence of metastases to bone in cases of carcinomas of the prostate, breast, stomach, kidney, and thyroid, the neoplasms which are most likely to metastasize to bone. Piney and Hamilton-Paterson have pointed out that it is surprising how often tumor cells are found in the sternal marrow of patients with malignant neoplasms, even in the absence of clinical and roentgenographic evidence of metastasis. They suggest that the routine use of sternal aspiration might disclose that many cases thought to be operable have already passed through the stage in which cure is possible. Along this same line, Henning recently advocated using bones other than the sternum and choosing a site for aspiration on the basis of the presence of tumor nodules, roentgen abnormalities, or areas of bone pain.

Dr. Pascher's work has demonstrated that sternal aspiration is a valuable diagnostic procedure in a variety of skin diseases. In a few of these conditions, as those encountered in other branches of medicine, examination of marrow is sufficient to establish the diagnosis, but more frequently bone marrow study must be utilized as a method of confirming the clinical diagnosis in conjunction with other accepted diagnostic procedures.

Dr. Frances Pascher, Brooklyn: I should like to add that we performed 94 punctures in 84 patients without mishap. However, one must be very careful to exclude patients with a history of coronary thrombosis or arteriosclerosis of the coronary arteries.

GNATHOSTOMIASIS IN JAPAN

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TOKYO, JAPAN

THIS BRIEF discussion of gnathostomiasis in Japan will start with the history of so-called Yangtze edema.

Yangtze edema (*chōkō-fushu* in Japanese) during the past 50 years has occasionally occurred among Japanese people who lived in the Yangtze Kiang Valley in China. In 1902 Yamada [1] interpreted it as Quincke's acute circumscribed edema [2] because of the migrating intermittent swellings of the skin. Later it was regarded as a food allergy, for it occurs usually in people who have eaten uncooked fresh-water fish caught in the Yangtze district. Komaya, who studied this disease for years in Shanghai, pointed out some clinical differences between Yangtze and Quincke's edemas. He noted particularly the presence of superficial indurated areas and progressively extending linear eruptions and swellings in some cases of Yangtze edema. In general, the swellings of Yangtze edema are more compact, brighter red, and more inflammatory than the edematous, rather pale swellings of Quincke's edema. The swellings migrate as do those of Quincke's edema but as a rule remain localized for several days, while swellings of Quincke's edema appear and disappear more quickly. From the clinical features of Yangtze edema, Komaya theorized that the disease was caused by small parasites which creep about at various depths in the skin and/or sometimes remain localized. In 1944-1945, he excised some of the edematous lesions and sent them to me for histologic examination. In 4 of 11 cases of Yangtze edema, microscopic examination of the skin showed a larva and marked tissue eosinophilia. The larvae were morphologically identical with those of Gnathostoma spinigerum Owen (1836). While the histologic examination was in progress, Komaya [3] discovered that 3.9% of cats and 0.9% of dogs in Shanghai have adult worms of G. spinigerum in the gastrointestinal tract. *Raigyo* (Ophicephalus argus Cantor), *ketsugyo* or *keigyo* (Siniperca chuatsi Basilewsky), and two other kinds of fish often have encysted larvae of this worm in their muscles and livers. It has been known that the edematous skin lesions occur several days or weeks after the eating of these uncooked fish.

In view of these findings, Komaya, Kitamura, and Komiya [4] came to the conclusion that Yangtze edema is due to G. spinigerum. The infection results from

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1. Yamada, H.: Jap. J. Dermat. & Urol. **2**:119, 1902.

2. Quincke, H.: Monatsh. prakt. Dermat. **1**:129, 1882; Med. Klin. **17**:675, 705, and 721, 1921.

3. (*a*) Komaya, G.; Kitamura, K., and Komiya, Y.: Shanghai Shizenkaguku Kenkyūjo Ihō **15**:1, 1945. (*b*) Komaya, G.; Kitamura, K.; Komiya, Y., and Kondō, S.: ibid. **15**:5, 1945.

4. Komaya, G.; Kitamura, K., and Komiya, Y.: Rinshō no Hifu to Hitsunyō **10**:295, Plate 101, 1944.

eating raw fresh-water fish containing the encysted larvae of this worm. Yangtze edema is similar to *tua chid*,[5] which is seen in Siam and which has skin lesions resembling those of Yangtze edema. *Tua chid* is caused by the eating of Ophicephalus striatus Bloch and other fresh-water fish, which were found to be the second intermediate hosts of G. spinigerum. Of *tua chid* it is believed that the Gnathostoma larvae which have been ingested go from the stomach to the skin and give rise to swellings and other lesions in the skin. A similar process may cause the skin lesions of Yangtze edema. Serious complications, such as blindness, intermittent convulsions, hemoptysis, and hematuria, are seen frequently in patients with *tua chid* and are considered to result from the localization of the larvae in the affected organ. However, such serious manifestations do not exist in Yangtze edema.

It may be recalled that from 1919 to 1923 larvae of G. spinigerum were removed from three cases of creeping eruption,[6] all the patients being Japanese who had been in the Yangtze district. However, few investigators suspected the relation of Yangtze edema to this worm until we found its larvae in the skin lesions of this disease, as well as in the fishes above mentioned.

The presence of Genus Gnathostoma Owen (1836) in Japan was confirmed by sporadic discoveries of adult worms of Gnathostoma hispidum Fedchenko (1872) in some domestic animals. Yoshida[7] found G. spinigerum in weasels (Lutreola itatsi itatsi). In 1940-1941, Yamaguti,[8] who studied the adult worms and eggs of Yoshida's G. spinigerum in weasels, renamed it Gnathostoma nipponicum n. sp. Miyazaki and Umetami recently[9] found adult worms of Gnathostoma in weasels and larvae in frogs (Rana nigromaculata Hallowell), as well as in a leach (Misgurnus anguilli caudatus Cantor).

There have been no reports of gnathostomiasis in Japan except for Kinoshita's case of creeping disease,[10] from which the larva of G. hispidum was extirpated. There are two kinds of gnathostomiasis among Japanese at present. One form is Yangtze edema, or *tua chid*, which was acquired while the patient was temporarily residing in China, Thailand, or some other Asiatic country. The other form is clinically identical to Yangtze edema but occurs in patients who have never lived outside Japan. The former or so-called exotic gnathostomiasis may be observed for several years because swellings and other skin lesions may recur at intervals of two or three years, as we have seen in several cases. The following two cases are presented as examples of the latter or so-called native gnathostomiasis.

CASE 1.—A 14-year-old Japanese boy, born in Kitagata in Saga Prefecture, Kyūshū, had never been abroad. On Oct. 16, 1944, he ate raw fish called *Taiwan-dojō* which were caught in a stream near his home. The next day, the boy felt nauseated and generalized urticaria developed. No other member of his family experienced any ill-effects from eating the raw fish. Attacks of urticaria recurred three times during the next week. Three weeks after he ate the fish, a

5. Daengsvang, S.: The Life-Story of "Tua Chid" (Gnathostoma Spinigerum), J. Thailand Research Soc. Nat. Hist. (Supp.) **12**:161, 1939; J. Parasitol. **35**:116, 1949.

6. (*a*) Tamura, H.: Jap. J. Dermat. & Urol. **19**:827 and 891, 1919. (*b*) Ikegami, Y.: Ibid. **19**:838, 1919. (*c*) Morishita, K.: Ibid. **23**:732, 1923.

7. Yoshida, S.: Nisshin Igaku **20**:1604, 1931.

8. Yamaguti, S.: Jap. J. Zool. **9**:409, 1940-1941.

9. Miyazaki, I., and Umetami, K.: Rinshō to Kenkyū **27**:112, 1950; Igaku to Seibutsugaku **16**:115, 1950.

10. Kinoshita, M.: Jikken Ihō **10**:911, 1924. Morishita.[6c]

pruritic, slightly tender, egg-sized swelling appeared on the right hypochondrium. It disappeared after 10 days, only to reappear on the left hypochondrium, where it stayed for 10 days and then again disappeared. Two days later, the skin of the abdomen became indurated, erythematous, and swollen. The boy's father had read in the newspaper about our studies on Yantze edema and had noted the presence of localized swelling of the boy's skin similar to those of

Fig. 1 (Case 1).—Arrow indicates palm-sized swelling, slight scaling, and excoriations on a superficial, linear, indurated band (abdomen).

Fig. 2.—*Taiwan-dojō* (Ophicephalus argus), caught in Kitagata.

Yangtze edema seen among his neighbors, who had allegedly contracted the disease after eating *Taiwan-dojō*, which had recently begun to appear in Kitagata.

Clinically, the patient was well developed and well nourished. The entire abdomen was tense. In the left lower portion of the abdomen there was a pruritic, oval, erythematous, firm, palm-sized swelling. Lateral and superior to this swelling there were two cord-like, intracutaneous indurations which were parallel to each other. On the surface of one of these

indurated bands were found small areas of excoriations and desquamation (Fig. 1). The leucocyte count was 16,500, with an eosinophilia (45%). An encysted larva of G. spinigerum was found in the muscles of a *Taiwan-dojō* which had been brought from Kitagata to us and had been identified with Ophicephalus argus (Figs. 2, 3, and 4).

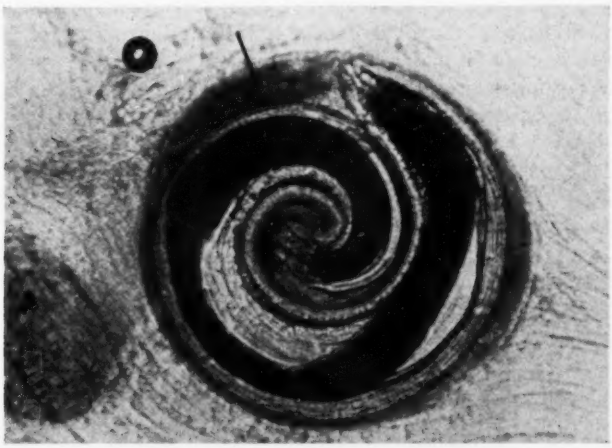

Fig. 3.—Encysted larva of G. spinigerum, embedded in the muscles of fish in Figure 2; arrow indicates esophagus.

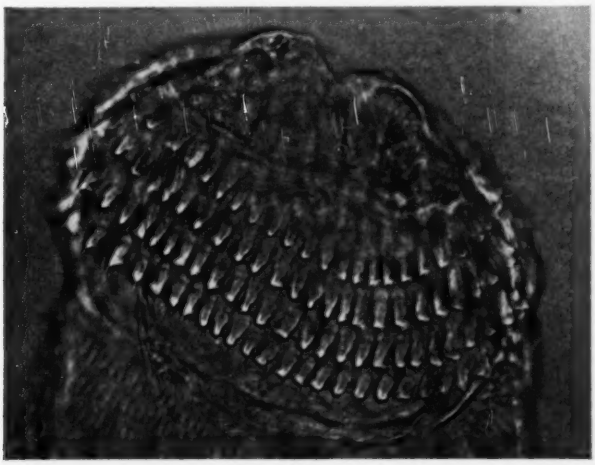

Fig. 4.—High-power magnification of cephalic bulb of the larva shown in Figure 3, dissected out from cyst, dehydrated, clarified in xylene, and mounted with balsam. It contains lips with papillae on its apex and four transverse rows of single-pointed spines on its side wall.

After this case was reported by Yoh [11] in 1946, it was soon discovered that in various other places in Kyūshū there were instances of this disease after the eating of Ophicephalus argus, which is called *Taiwan-dojō, raigyo,* or *rai.* Epidemics of

11. Yoh, Y.: Rinshō to Kenkyū **23**:93, 1946.

this disease have also been reported.[12] S. Kitamura[13] was of the opinion that the skin lesions are not necessarily caused by Gnathostoma larvae themselves but may also develop as the result of reaction to other related allergens. It is said that there are now two species of the Family Ophicephalidae in Japan. One, Ophicephalus tadianus Jordan et Evermann, was imported about 1906 from Formosa. The other, Ophicephalus argus, was brought here about 1926 from China. Both of these species are called *Taiwan-dojō* (it means "loach of Formosa"), *raigyo*, or *rai*, but the fish which is propagating at present in many places of Japan and is eaten by Japanese belongs mostly to Ophicephalus argus.

Fig. 5 (Case 2).—Gnathostoma larva, surrounded by numerous eosinophiles, is located in lower portion of corium. Specimen was removed from superficial indurated band on right cheek.

From 1904 to 1918, cases were reported[14] of acute circumscribed edema occurring among Japanese people who lived in Formosa. These cases are noteworthy because they occurred in Formosa where Ophicephalus tadianus and some other species of Ophicephalidae breed. A history of eating shrimps was usually obtained.

In 1941, Abe[15] reported cases of acute circumscribed edema which occurred in Hokuriku district (Middle Japan) after the eating of *keigyo*, a fish allegedly imported from China. As already mentioned, in 1945, Komaya[3b] reported that this fish is often infected with G. spinigerum.

12. Misao, T., and Hattori, J.: Nihon Igaku **3416**:151, 1947. Kitamura, S.; Ichinose, K., and Nōtomi, N.: Jap. J. Dermat. & Urol. **57**:63, 1947.

13. Kitamura, S., and Nōtomi, N.: Jap. J. Dermat. & Urol. **58**:78, 1948.

14. Nagano, J.: Taiwan igakkai zasshi **27**:425, 1904. Nambu, K.: Ibid. **188**:687, 1918.

15. Abe, T.: Jap. J. Dermat. & Urol. **52**:160, 1942.

In Tokyo since 1946 patients have been seen who have gnathostomiasis apparently acquired while traveling abroad. Other patients were seen who had Yangtze-edema-like symptoms for the first time after they ate *raigyo* in Tokyo and its vicinity. No Gnathostoma larva has been discovered in some 30 examples of *raigyo* from several sources in the Tokyo area. In the following case, a Gnathostoma larva was histologically found in a cutaneous lesion.[16]

CASE 2.—From 1943 to 1944 a 28-year-old day laborer had been in Manchuria, where he denied eating *raigyo* and had no Yangtze-edema-like symptoms. In 1944 he returned to Tokyo, since when he has eaten *raigyo* very often. Cutaneous swelling appeared for the first time in May, 1945, in the right axilla, in August, 1945, on the abdomen, in March, 1946, on the right side of the chest, and in October, 1948, on the face. Since then the swelling has been confined to various areas on the face and head. In May, 1949, when the patient came to us for the first time, there was a palm-sized indurated swelling located on the right cheek. The leucocyte count was about 10,000, the eosinophile count being about 21%. Two weeks later, another swelling appeared near the right angle of the mouth. A rice-grain-sized induration in the center of the swelling was excised and examined histologically. A Gnathostoma larva was found in the lower layer of the corium, and there was a dense infiltrate of eosinophiles (Fig. 5).

As for the prevention of gnathostomiasis, the eating of uncooked Ophicephalus argus should be avoided. As for treatment, there is, as yet, no effective method except surgical removal of the cutaneous lesions. Surgical treatment may fail when the larvae lie concealed in the depths of relatively large lesions. Treatment with antimony preparations is ineffective.

16. Kitamura, K., and Kawai, H.: Nibon Iji Shimpō **1326**:1924, 1949. Kawai, H.: Rinshō Hifuka Hitsunyōkika **4**:420, 1950.

ZIRCONIUM SALTS IN PREVENTION AND TREATMENT OF RHUS TOXICODENDRON DERMATITIS

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SYRACUSE, N. Y.

THE USE of zirconium salts in treatment of poison-ivy dermatitis has previously been reported.[1] The purpose of this paper is to present further laboratory experiences which justify the conclusion that certain zirconium salts are beneficial in prophylaxis and treatment of Rhus toxicodendron dermatitis.

EXPERIMENTAL STUDY

The following experiments were performed on volunteers known to be sensitive to Rhus toxicodendron in an attempt to understand further the action of various zirconium salts on urushiol. All volunteers gave a history of one or more attacks of poison-ivy dermatitis, and their sensitivity was proved when a typical dermatitis developed after the cutaneous application of Rhus toxicodendron extract in a 1:10 mixture with acetone in the laboratory. Erythema and papules were apparent within 24 to 48 hours after application of the extract. The amount of extract applied in all experiments was limited to that adhering to the end of a 2-mm. wooden stick. This method usually resulted in the formation of a satisfactory dermatitis, but the cutaneous destruction which can result from large doses was avoided.

The first phase of experimentation was an attempt to determine the in vitro effects of zirconium salts on urushiol. The zirconium salts used were prepared in a 10% aqueous solution. Mixtures of 0.25 cc. of urushiol (1 part in 10 parts acetone) were made with 2 cc. of the zirconium salt solution. An immediate precipitate was formed. This was allowed to stand for 15 minutes at room temperature (23 to 25 C.) and was then filtered through standard No. 40 filter paper.

Next the agents were applied to the cutaneous areas of the volunteers in a standard manner and the results recorded.

Area	Agent
1 (upper left)	Urushiol in a 1:10 mixture with acetone (control)
2 (upper right)	Zirconium salt being used
3 (lower left)	The precipitate
4 (lower right)	The filtrate

It was then possible to divide the zirconium salts used into two groups, according to their ability to alter urushiol. Group I, which included zirconium acetate, lactate, and sulfate, caused an immediate physical change in the urushiol by precipitation and, at the same time, a concentration of the toxic principle in the precipitate. Aside from this concentration, there was no demonstrable alteration in the urushiol.

Figure 1 demonstrates a typical reaction from the zirconium salts in this group. Area 3 reveals a large area of dermatitis as compared with Area 1, the control. Area 4, on which the filtrate in the experiment was applied, shows some dermatitis. It is possible to remove the toxic

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This study was aided by grants from Ciba Pharmaceutical Products, Inc., Summit, N. J., and Titanium Alloy Manufacturing Company, Niagara Falls, N. Y.

1. Cronk, G. A., and Naumann, D. E.: Zirconium Treatment in Ivy Poisoning: Preliminary Investigation, J. Lab. & Clin. Med. **37**:909, 1951.

principle completely from the filtrate by the addition of a sufficient amount of the precipitating agent. It was demonstrated previously by many observers [2] that other agents also have this property.

Group II included hydrous zirconium oxide, zirconium hydrate carbonate, sodium zirconium glycolate and, to a less extent, zirconium oxychloride. These agents, like those in Group I, readily precipitate urushiol. After the original procedure, these agents were applied to Rhus-toxicodendron-sensitive skin. The results of the experiment with hydrous zirconium oxide are shown in Figure 2. It will be observed that the precipitate and the filtrate both failed to cause a dermatitis. Zirconium oxychloride produced a similar failure when freshly prepared. However, this salt is extremely unstable and rapidly loses its power to inactivate in an aqueous solution or

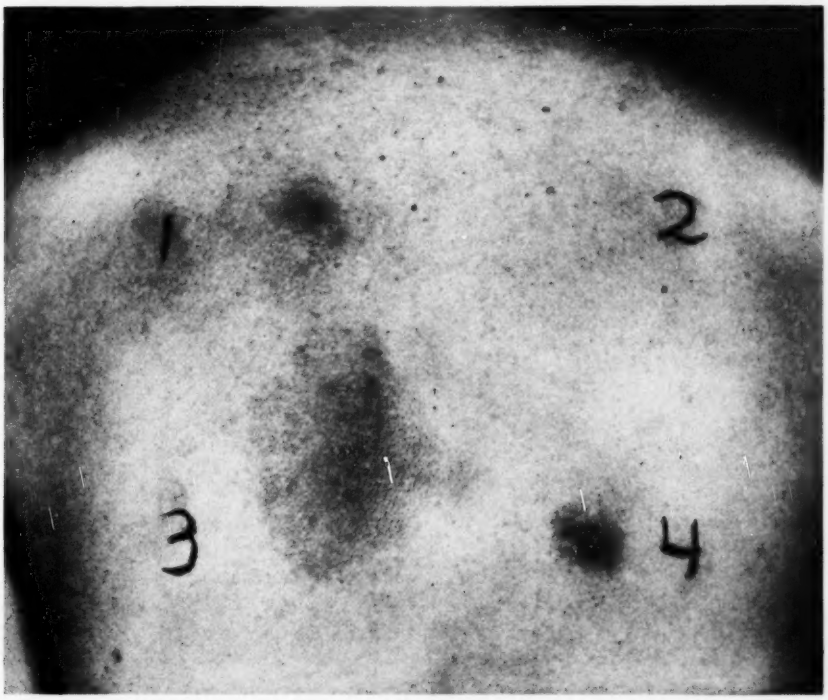

Fig. 1.—Typical reaction from zirconium salts in Group I. Zirconium salt was used in Area 2. Precipitate applied in Area 3 caused large area of dermatitis as compared with Area 1, the control. Area 4, in which the filtrate was used, shows some dermatitis.

when exposed to the atmosphere. These results were obtained from 10 experiments on five volunteers.

The second phase of experimentation was designed to see whether hydrous zirconium oxide was effective in the prevention of dermatitis after contact with oleoresin. For these experiments the chemicals used were in an essentially neutral base consisting of (1) sodium lauryl sulfate, (2) glyceryl monostearate, (3) stearyl alcohol, (4) glycerin, (5) emulsified wool fat (lanolin), and (6) white petrolatum.

2. Gisvold, O.: The Effects of Some Adsorbents, Precipitants and Oxidants upon the Resin of Rhus Toxicodendron, J. Am. Pharm. A. (Scient. Ed.) **30**:17, 1941.

Rhus toxicodendron extract in a 1:10 mixture with acetone was applied to five separate areas on the volunteer's back. Figure 3 shows the reactions observed when various ointments were applied one hour after the application of urushiol.

Area	Application
1	Untreated control
2	Ointment containing 2% tripelennamine hydrochloride and 5% hydrous zirconium oxide
3	5% hydrous zirconium oxide ointment
4	2% tripelennamine hydrochloride ointment
5	Ointment base as a placebo ointment

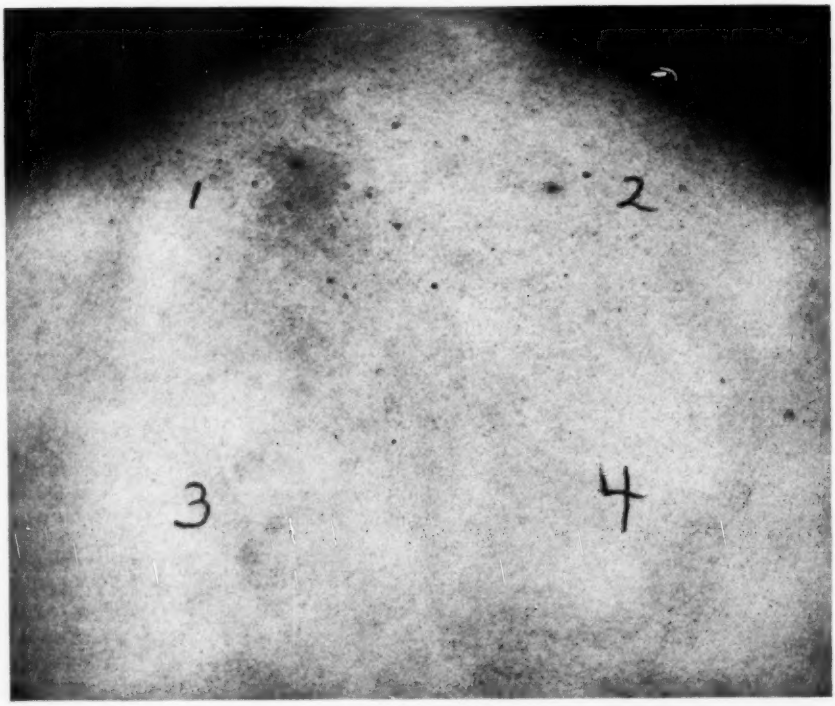

Fig. 2.—Reaction from hydrous zirconium oxide (Group II) applied in Area 2. Both precipitate (applied in Area 3) and filtrate (applied in Area 4) failed to cause a dermatitis. Area 1 is the control.

No dermatitis developed in Areas 2 and 3. A typical Rhus dermatitis developed in Areas 1, 4, and 5.

It has been observed from several similar experiments that, up to one hour after contact with urushiol, 5% hydrous zirconium oxide and hydrous zirconium oxide with tripelennamine (pyribenzamine®) hydrochloride will prevent the development of a Rhus dermatitis. Tripelennamine ointment alone does not have this effect on urushiol. It is entirely possible that the time interval within which treatment is effective exceeds one hour. This has not, however, been established yet in this laboratory.

CHEMISTRY OF URUSHIOL

The understanding of the chemistry of poison ivy's active ingredient was initiated by the work of Toyama,[3] who demonstrated that its violent, vesicant action was dependent upon intact hydroxyl groups. In 1934 Hill and others [4] established that urushiol was an orthodihydroxybenzene compound containing an unsaturated hydrocarbon in the No. 3 position (Fig. 4). Other investigators [5] confirmed the fact

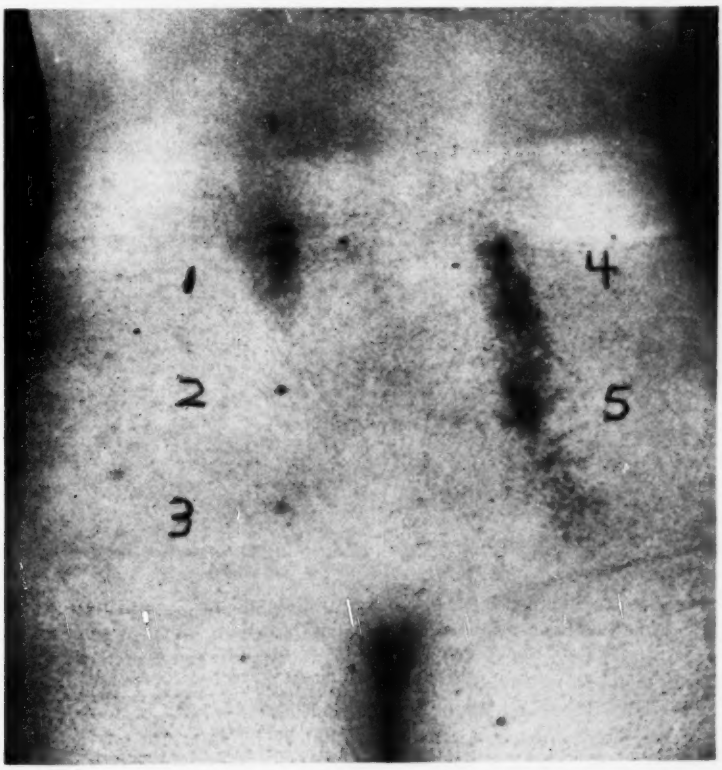

Fig. 3.—Reactions observed when various ointments of hydrous zirconium oxide were applied one hour after application of urushiol. No dermatitis developed in Areas 2 and 3, on which ointment containing 2% tripelennamine hydrochloride and 5% hydrous zirconium oxide and 5% hydrous zirconium oxide ointment were applied respectively. A typical Rhus dermatitis developed in Area 1 (untreated control) and in Areas 4 and 5, which were applied 2% tripelennamine hydrochloride ointment and ointment base as a placebo ointment, respectively.

3. Toyama, I.: Rhus Dermatitis, J. Cutan. Dis. **36**:157, 1918.

4. Hill, G. A.; Mattacotti, V., and Graham, W. D.: The Toxic Principle of Poison Ivy, J. Am. Chem. Soc. **56**:2736, 1934.

5. Mason, H. J., and Schwartz, L.: Toxic Principles of Poison Ivy, J. Am. Chem. Soc. **64**:3058, 1942. Keil, H.; Wasserman, D., and Dawson, C. R.: Relation of Chemical Structure in Pyrocatechol Compounds and Derivative of Poison Ivy Hypersensitiveness in Man as Shown by Patch Test, J. Exper. Med. **80**:275, 1947. Shelmire, B.: Nature of the Excitant of Poison Ivy Dermatitis, Arch. Dermat. & Syph. **42**:405, 1940; The Poison Ivy Plant and Its Oleoresins. J. Invest. Dermat. **4**:337, 1941.

that this phenolic compound, urushiol, is the active ingredient of Rhus toxicodendron.

A great many research projects published in the past 30 years and using various chemicals to inactivate urushiol in vitro and in vivo helped in understanding the chemistry of this agent. It was observed in the 1930's [2] that many agents, like ferric chloride, had the ability to precipitate urushiol but were unable to inactivate the toxic principles involved. A variety of adsorbing agents was also tried unsatisfactorily. The most gratifying results have been obtained with chemicals which alter the hydroxyl groups of urushiol. Oxidizing agents, such as sodium perborate,[6] sodium peroxide, hydrogen peroxide, and potassium permanganate,[7] have been found to have an inactivating effect, but a limited clinical application. Enzymes, such as tyrosinase,[8] have also been reported as inactivating the toxic principle of urushiol. Of these several agents, few have found widespread use, particularly because of their instability and difficulty in application.

USES OF ZIRCONIUM [9]

The element zirconium is found in abundance widely distributed over the earth's surface. Because of its many physical and chemical properties, it has found extensive use in industry and recently also in the medical field.

Zirconium salts are thermal-stable. They have a high melting point (zirconium carbide, 3,532 C.), a high specific gravity, and the ability to combine with many

Fig. 4.—Structural formula of urushiol.

radicals (such as hydroxyl groups and amino acids) and to form hydrophobic soaps when combined with fats.

These characteristics make zirconium useful in the production of ceramic enamels, insulating furnaces, filaments for incandescent lamps, and crucibles and molds for aluminum ingots. In the fabric industry zirconium salts are used to stabilize dyes and to render material water-repellent.

Schubert,[10] working at Argonne National Laboratory, Chicago, has demonstrated a potentially important use of zirconium in its ability to increase excretion of plutonium from animal tissue. Current investigation has also suggested that zirconium salts, by removing fatty acids, may act as a deodorant.

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6. Shelmire, B.: Sodium Perborate Ointment in Poison Ivy Dermatitis, J. A. M. A. **116**: 681, 1941.

7. Gisvold.[2] Schwartz, L.; Dunn, J. E., and Goldman, F. H.: A New Base for the Protective Ointment for the Prevention of Poison Ivy Dermatitis, Pub. Health Rep. **57**:578, 1942.

8. Sizer, I., and Prokesch, C. E.: Destruction by Tyrosinase of the Irritant Principles of Poison Ivy and Related Toxicants, J. Pharmacol. & Exper. Therap. **84**:363, 1945.

9. Blumenthal, W.: Some Features of Zirconium Chemistry, J. Chem. Ed. **26**:472, 1949; Zirconium Chemicals: Their Application to Textiles, Part I, Rayon & Synthetic Textiles **31** (No. 12):81, 1950; Their Use in Water-Repellent Treatment of Textiles, Part II, ibid. **32** (No. 1):85, 1951; Hygienic Aspects of Treating Textiles with Zirconium Chemicals, Part III, ibid. **32** (No. 4):79, 1951.

10. Schubert, J.: Treatment of Plutonium Poisoning by Metal Displacement, Science **105**: 389, 1947.

COMMENT

The basic reactions involved in the inactivation of urushiol by certain zirconium compounds are not clearly understood at this time. Two definite phenomena apparently occur when such compounds as hydrous zirconium oxide come in contact with urushiol: The first is a physical reaction in which a precipitate is formed; the second is a chemical alteration of the urushiol. This chemical reaction has been suggested by Blumenthal [11] to be one of chelation of the hydroxyl groups and can be represented as in Figure 5.

When urushiol comes into contact with a sensitized skin, apparently a variable period elapses between the time of contact and the time at which the toxic phenol becomes fixed to the protein of the skin. This time period is dependent on such factors as individual sensitivity to and dosage of Rhus toxicodendron. There also appears to be a saturation level for a given area of skin. Not infrequently, an excess of oleoresin is present in a given area which can be, and is, transmitted to unaffected areas of skin, causing a spreading dermatitis.

These facts and the current experiments suggest that the main effect of zirconium oxide is one of chemical neutralization of the free oleoresin of poison ivy. This would lead to the conclusion that zirconium oxide can best be applied clinically for (1) prophylaxis, (2) removal of excess oleoresin from supersaturated areas and,

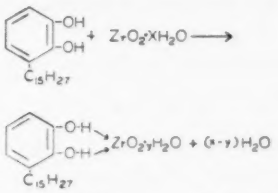

Fig. 5.—Reaction involved in inactivation of urushiol by certain zirconium compounds.

thus, prevention of further skin damage in other areas, and (3) prevention of dermatitis after contact.

The possibility that zirconium salts may have a further action in poison-ivy dermatitis is suggested by the commercial use of these agents in the dye industry. It has been observed that zirconium ions have the ability to coordinate hydroxyl groups on the surface of proteins and become affixed to them.[11] Chemical reactions between zirconium salts and amino acids have also been observed—a phenomenon which may occur in vivo. These facts are applied in the dye industry, which uses zirconium salts to bind dyes to protein surfaces, such as hides and wool.

It can, therefore, at least be theorized that zirconium may compete with urushiol for the skin proteins and possibly reverses the urushiol-protein combination, making the oleoresin accessible for neutralization; but it must be kept clearly in mind that if a urushiol-protein combination in the skin exists for a sufficient time death of the cell unit will occur. In these circumstances the local problem becomes primarily one of tissue repair, and a dramatic therapeutic response to any agent cannot be expected. This reparative process will proceed at a more satisfactory rate if the excess toxic material is removed or neutralized, and, in my opinion, there is some advantage to using hydrous zirconium oxide even when the disease has advanced to the point of cellular death.

11. Blumenthal, W.: Personal communication to the author.

There is another physiological function of zirconium oxide as applied to cutaneous areas which may have a beneficial action in Rhus toxicodendron dermatitis. Of 88 patients with poison-ivy dermatitis treated in this clinic to date, 75% spontaneously drew attention to the fact that the pruritus of this dermatitis was relieved by the application of the zirconium preparation. Preliminary studies using standard thermal units suggest that hydrous zirconium oxide temporarily impairs the transmission of sensory impulses arising in cutaneous areas. It would appear that the antipruritic effect of this zirconium salt is about equal to that of 1% phenol in calamine lotion.

SUMMARY

Controlled experiments have demonstrated that hydrous zirconium oxide, zirconium hydrate carbonate, sodium zirconium glycolate, and zirconium oxychloride will precipitate and inactivate urushiol in vitro. In contrast, zirconium sulfate, acetate, and lactate precipitate urushiol but do not inactivate the toxic principle. The reason for this difference is not yet understood.

Hydrous zirconium oxide when applied one hour after contact with the oleoresin will prevent the development of Rhus toxicodendron dermatitis; but it cannot reverse cellular death from the toxic oleoresin.

In ointment form, hydrous zirconium oxide is stable when placed in proper containers and may easily be applied. Its therapeutic results, within the above limitations, are dependable.

No evidence of toxicity from cutaneous application of zirconium salts was noted.

CONCLUSIONS

Zirconium sulfate, acetate, and lactate cause in vitro precipitation, but not inactivation, of urushiol.

Hydrous zirconium oxide, zirconium hydrate carbonate, and sodium zirconium glycolate cause in vitro precipitation and inactivation of urushiol.

Hydrous zirconium oxide and hydrous zirconium oxide with tripelennamine (pyribenzamine®) hydrochloride will prevent the development of Rhus toxicodendron dermatitis when applied to urushiol-treated sensitive skin one hour after the poison-ivy-extract application.

Hydrous zirconium oxide has definite antipruritic properties.

No evidence of toxicity was observed from the cutaneous application of several zirconium compounds.

Dr. Dorothy E. Naumann assisted in preparation of this manuscript.

Clinical Notes, New Instruments and Techniques

DERMATITIS VENENATA DUE TO POTASSIUM UNDECYLENATE

SIDNEY I. ROGERS, M.D.
AND
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BRONX, N. Y.

We have recently seen a case of dermatitis venenata due to potassium undecylenate. We have been unable to find any previous report of dermatitis venenata due to undecylenic acid or its salts. In view of the widespread use of these substances in the local treatment of dermatophytosis, we feel that the possibility of one of these agents producing a contact dermatitis should be made known.

REPORT OF A CASE

J. B., a 52-year-old white man, had intermittent scaling and itching between the toes. He applied timofax® ointment (a cream containing 10% undecylenic acid as free acid and potassium salt) to the feet on two successive days, and on the third day the dorsa of the feet became erythematous, edematous, and exudative. Application of the ointment was discontinued, and there was gradual healing with soothing local therapy. There were slight residual erythema and fissuring at the base of the left third toe after 10 days. He again applied timofax® ointment to the feet, and within 24 hours marked erythema, edema, and pruritus developed on the toes and dorsa of the feet. Use of the ointment was again discontinued, but response to soothing therapy was much slower. It was three weeks before pruritus disappeared and the feet were clear of lesions.

Patch tests with materials from the patient's shoes gave negative results. Timofax® ointment and powder patch tests gave marked positive reactions. The compounds in common in the timofax® powder and the ointment are undecylenic acid, potassium undecylenate, methyl salicylate, and eucalyptus oil.[1] Undecylenic acid was not considered the offending agent, since patch tests with other preparations containing undecylenic acid gave negative reactions. Results of patch tests performed on the patient with 2% methyl salicylate and 1% eucalyptus oil were negative. Patch tests with potassium undecylenate powder gave a marked positive reaction. Controls patch-tested with potassium undecylenate powder showed no reactions, indicating that this salt is not a primary irritant in the strength used for patch testing. The patient was also patch-tested with preparations containing zinc undecylenate and copper undecylenate, and also with potassium chloride and potassium permanganate. Reactions to these tests were all negative, thus ruling out the possibility of sensitization to the potassium or undecylenate fractions per se in potassium undecylenate.

SUMMARY

A case of dermatitis venenata due to potassium undecylenate is reported. Sensitization to this salt and to other undecylenic acid salts is apparently very rare, judging by the scarcity of reports on such a condition.

From the Dermatology Section of the Veterans Administration Hospital, Bronx, New York.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Burroughs Wellcome & Company, Tuckahoe 7, N. Y., gave us the necessary information and supplied the potassium undecylenate for patch testing.

SUCCESSFUL TREATMENT OF GOLD DERMATITIS WITH CORTISONE GIVEN ORALLY

LOUIS G. JEKEL, M.D.
PHOENIX, ARIZ.

Although cortisone is not a panacea, it has been found to be useful in the treatment of a variety of diseases, including a number of cutaneous disorders. Record should be made of its benefits in different diseases when such are observed. My patient, suffering from gold dermatitis, improved rapidly while taking cortisone, after exhibiting no tendency to recover with symptomatic treatment for more than three months previously. Since gold dermatitis is potentially a dangerous disorder, the following report is made.

REPORT OF A CASE

Mrs. G. A., a 62-year-old white housewife, received injections of aurothioglucose (solganal® B in oil) for arthritis in three weekly treatments in May, 1951. The program was then interrupted until June 23, when weekly injections were again instituted. Late in July the patient complained of a sore mouth, with "blisters and raw spots." On Oct. 10, 1951, she received what proved to be her last injection of the gold preparation, for on the next day a widespread eruption developed which was most pronounced on the legs and forearms. At first the lesions were blisters, but later the new lesions became urticarial.

About six weeks later, on Nov. 27, the eruption having shown no tendency to clear, the patient was referred to me. Examination showed the patient to be in good general condition. She complained of moderately severe itching. The extensor surfaces of the forearms and legs were most severely involved. The cutaneous lesions were macules, papules, and slightly raised plaques. The newer lesions were red; the older lesions tended to be violaceous. There were some scaling, some excoriation, and, in some areas, considerable thickening of the skin with some lichenification. The lesions in the mouth were red, eroded areas. Thus, the eruption actually took on the appearance of erythema multiforme. The greatest inflammation was in certain areas on the legs where a preexisting varicose dermatitis was present.

The urine was normal. The blood count was normal except for eosinophilia (8 and 15% on two occasions).

The patient received symptomatic treatment in the form of an antihistaminic by mouth and an antipruritic shake lotion and ichthammol ("ichthyol") paste for topical application.

After two and one-half months of such treatment, the patient, although no worse, was not better. Therefore, a trial of cortisone therapy was ordered. One 25-mg. tablet was taken three times a day. Three days of such treatment showed such encouraging results that cortisone administration was continued, the dosage being reduced to 25 mg. twice a day. The condition showed steady improvement. At the end of four weeks, the eruption had cleared almost completely and the general condition of the patient was excellent.

SUMMARY

A patient with gold dermatitis is described who responded promptly and well to oral therapy with cortisone after she had not improved with symptomatic treatment.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

George H. Curtis, M.D., *President*

John R. Haserick, M.D., *Secretary*

Harold N. Cole Jr., M.D., *Reporter*

Sept. 27, 1951

Letterer-Siwe Disease. Presented by Dr. H. H. Bremers, Dr. C. George, and Dr. C. Sunit, for Dr. R. D. Mercer.

D. N., a white boy aged 12½ months, presents a purpuric eruption of three months' duration. He was hospitalized at Cleveland City Hospital from July 9 to 14, 1951. At that time he had a purpuric eruption over the face, on the distal extremities, and in the scalp, and there was a history of weight loss. There was a frequent dry cough, and the breath sounds were harsh. Hepatomegaly and cervical, axillary, and inguinal adenopathy were observed. A right inguinal lymph node biopsy showed moderate hyperplasia. A skin biopsy revealed chronic capillaritis and pericapillaritis. His weight was 9,200 gm.

The child was again hospitalized at Cleveland City Hospital from July 28 to Aug. 11, 1951, because of an intermittent temperature elevation to 102 F. and a cough. The rash was more pronounced than during the previous admission but was of similar distribution. He weighed 8,600 gm. Rhonchi were heard throughout the upper right chest. There were hepatomegaly and generalized adenopathy.

Urinalyses have given normal results. The total serum protein was 6.76 gm. per 100 cc., and the albumin-globulin ratio was 1.77. The serum potassium was 6.35 mEq. per liter. The total blood lipids were 430 mg. per 100 cc. The blood cholesterol was 133 mg. and cholesterol esters were 74.4 mg. per 100 cc. The serum phosphorus (inorganic) was 5.66 and 3.62 mg. per 100 cc. The alkaline phosphatase was 6.89 units. The hemoglobin concentration was 11.2 gm. per 100 cc. There were 4,660,000 red blood cells per cubic millimeter. White blood cell counts varied from 8,800 to 17,100, with a normal differential picture. Thrombocyte (platelet) counts varied from 84,000 to 535,620. The capillary clotting time was 3 minutes. The bleeding time was 3 minutes. The thymol turbidity was 4.5 units. The cephalin-flocculation test showed 1 unit. Serologic tests for syphilis were negative. Blood culture yielded no pathogens. Mercury, arsenic, and lead determinatiions on 24-hour urine specimens were negative. The absolute eosinophile count on July 31 was 0, and on Aug. 1 it was 4. A roentgenologic skeletal survey showed mild long bone osteoporosis, without evidence of a specific abnormality. The appearance of the chest was very strongly suggestive of a minimal early, diffuse nodular infiltration throughout both lung fields. The appearance was consistent with the clinical impression of changes due to lipid histiocytosis. Bone marrow studies were also done on July 13. One of us (R. D. M.) reported that the bone marrow then was essentially normal, with normal development of erythrocytes and cells of the leucocytic series. There were large numbers of giant cells which appeared to be varieties of megakaryocytes. Some were compatible with those of Letterer-Siwe disease, but there was nothing diagnostic about them. Bone marrow examination on July 31 revealed foam cells compatible with reticuloendotheliosis.

Skin and lymph node biopsies revealed characteristics mentioned above.

The child was given corticotropin, 15 mg. every six hours, from Aug. 1 through 10, 1951. The lesions on the hands and feet cleared. No change was noted in the liver size. Rhonchi were still heard in the chest, and the weight remained about the same.

DISCUSSION

Dr. H. N. Cole: This is apparently a typical case. Whether a typical Weber-Christian syndrome is going to develop in this child or whether he will die, as most of these children do, is very hard to say. These cases are very rare, and we are indebted to Dr. Mercer for the opportunity to see this patient.

Dr. E. S. Hallinger: I saw one other case. It involved a child 3 months of age, who lived only one month after the diagnosis was established. That child had a marked purpuric eruption,

which I believe this child showed originally but which is not evident today except around the shoulders and neck. The previous child had severe hepatosplenomegaly.

DR. I. L. SCHONBERG: The case is very interesting, and the findings fit in very well with the diagnosis. It is interesting that the child displayed a dermatitis after he left the hospital, because the usual type of dermatitis seen with Letterer-Siwe disease is of a sudden eruptive character. In several cases that I can recall, the eruption was of a crusted, exudative nature, usually present on the scalp and behind the ears. It is questionable whether the process this child has is associated with the disorder. Certainly the other findings are compatible with the diagnosis.

DR. H. Z. LUND: From the histologic standpoint, there is nothing to support the diagnosis of Letterer-Siwe disease. The lymph nodes certainly show nothing remarkable. I wondered if the skin biopsy specimen was representative, whether it was from one of the lesions or picked at random. We cannot confirm the diagnosis from what we have seen.

DR. H. H. BREMERS: A biopsy specimen was taken from one of the purpuric lesions. What did you think about the bone marrow?

DR. H. Z. LUND: As I recall the smear, Dr. Mercer saw some cells which he thought unusual but not diagnostic.

DR. H. H. BREMERS: Dr. Mercer had said that he thought he saw a few lipid cells.

DR. H. Z. LUND: Seeing a few cells containing lipid in the bone marrow is not necessarily diagnostic of Letterer-Siwe disease. We often see them in marrow, as in a fixed tissue preparation picked up by the needle. I don't think one can make a diagnosis of Letterer-Siwe disease on the basis of the presence of foam cells alone. The cells are not sufficiently characteristic.

Case for Diagnosis: Flat Warts? Presented by DR. JOHN A. GAMMEL.

R. U., 5 years old, was observed at birth to have a definite bulbous enlargement of the nose, which has not changed to any noticeable degree.

About one year ago tiny, skin-colored, flat papules, about 1 mm. in diameter, developed near the tip of the nose. During the following months new ones appeared on the tip of the nose and the septum.

When the patient was first seen, on March 27, 1951, a general soft enlargement of the nose was noted. There were about eight pinhead-sized flat papules on the tip of the nose and on the septum.

Urinalysis revealed no abnormality. Permission for a biopsy could not be obtained.

The patient received 75 r at 60 kv. and two and four weeks later received doses of 50 r. Mercury with chalk, 1 grain (0.06 gm.) three times a day, was given orally for about six weeks. In June and July carbon dioxide snow was applied on two occasions with light pressure.

There have been no new lesions in recent months, and the existing lesions have become less conspicuous.

DISCUSSION

DR. G. A. DE OREO: I offer the diagnosis of sebaceous nevus. I think the color, plus the history that this was present at or shortly after birth, would be consistent with that diagnosis. The midline is a favored site. This nevus is frequently found in the center of the face, around the nose.

DR. E. ARDAY, Rocky River: Of course, I understand the difficulties of obtaining a biopsy specimen in this particular location in a child, but I think this is probably a nevoxanthoendothelioma rather than a sebaceous nevus. It is not punctate, like a sebaceous nevus. I do not know how the question can be decided, but the soft compressible tumor-like structure is very much like a nevoxanthoendothelioma.

DR. I. L. SCHONBERG: I think this patient may have had a hemangioma with a superimposed verruca plana juvenilis.

DR. H. G. PARKHURST, Toledo: I thought this was a deep angioma, possibly a hemolymphangioma, which is now subsiding after the irradiation.

DR. J. A. GAMMEL: When I first saw this case, the enlargement of the nose was what impressed me most, and there were, in addition, several small papules. Several of the lesions were removed by electrosurgery, but they returned immediately; therefore, the surgeon and

the family physician referred the patient to me. I thought at first that these lesions were warts and treated them with mercury with chalk and sulfur preparations locally, but there was no response. At one time I thought it was a lymphangioma, but the picture has gradually changed. If anyone has any suggestions concerning therapy, they will be greatly appreciated.

DR. G. W. BINKLEY: I think that before any further treatment can be undertaken, a biopsy specimen should be obtained.

Ichthyosis Congenita (Mild Type). Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for the Department of Pediatrics, University Hospitals.

R. K., a boy approximately 2½ months old, exhibited at birth a collodion-like integument over the entire body, with ectropion, puckering of the mouth, and distortion of the ears. The child was born one month prematurely and weighed 2,160 gm. Gradually the collodion-like layer was exfoliated. The eyelids, mouth, and ears became normal. The underlying epidermis was scaly and slightly erythematous.

There is no familial history of any similar skin disease. Serologic tests for syphilis (maternal) were negative.

The child was last seen more than a month ago. At that time remnants of the collodion-like layer remained on the scalp and chest. There were generalized scaling, dryness, and slight erythema of the skin. The physical examination otherwise gave normal results.

The hemoglobin concentration was 17 gm. per 100 cc. There were 4,530,000 red blood cells and 20,050 white blood cells per cubic millimeter, with 50% segmented neutrophiles, 45% lymphocytes, and 5% eosinophiles.

Sections of the skin taken when the collodion-like layer was present show a moderately thick layer of acidophilic-staining dense keratin on the surface of the epidermis. In some foci it extends into the pilosebaceous orifices.

The child was hospitalized for three weeks following delivery. He was kept in an incubator and was given penicillin orally, chloramphenicol (chloromycetin®), and an evaporated milk formula. Cold cream and liquid petrolatum were used on the skin.

DISCUSSION

DR. H. N. COLE: I have seen four or five cases of the harlequin fetus. These infants usually look as though they are encased in collodion, and in most cases they die. This is the only one I can remember that has come through, and I believe that this child is going to live. If the infants get rid of the outer casing, they survive. It is a very unusual case. The pictures that Dr. Bremers succeeded in obtaining are excellent examples of the child's appearance when he was first seen.

Case for Diagnosis: Parapsoriasis en Gouttes (Brocq)? Presented by DR. HAROLD N. COLE, DR. J. R. DRIVER, and DR. HAROLD N. COLE JR.

Elephantiasis Nostras. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. HAROLD N. COLE and DR. J. R. DRIVER.

Lymphangioma. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. R. SCOTT.

Pemphigus Erythematosus (Senear-Usher Syndrome) in an Involuting Stage. Presented by DR. GEORGE M. STROUD.

Linear Scleroderma. Presented by DR. ALLEN E. WALKER, Bay Village, and (by invitation) DR. JOHN J. STEWART.

Generalized Scleroderma. Presented by DR. E. R. BRODY, Youngstown, DR. A. R. CUCKERBAUM, and DR. H. H. BREMERS.

Lichen Sclerosus et Atrophicus. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. HAROLD N. COLE and DR. J. R. DRIVER.

Parapsoriasis en Plaques. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. HAROLD N. COLE and DR. J. R. DRIVER.

Lichen Urticatus. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. HAROLD N. COLE and DR. J. R. DRIVER.

Lichen Striatus. Presented by DR. HAROLD N. COLE, DR. J. R. DRIVER, and DR. HAROLD N. COLE JR.

Melanosis (Mucous Membrane). Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. HAROLD N. COLE and DR. J. R. DRIVER.

Pemphigus Erythematodes. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. HAROLD N. COLE and DR. J. R. DRIVER.

Case for Diagnosis: Lupus Erythematosus? Presented by DR. E. H. JONES, Warren, and DR. E. H. JONES JR.

Necrobiosis Lipoidica. Presented by DR. E. H. JONES, Warren, and DR. E. H. JONES JR.

Case for Diagnosis: Dermatofibroma? Dermatofibrosarcoma Protuberans? Nodular Subepidermal Fibrosis? Presented by DR. HAROLD N. COLE, DR. J. R. DRIVER, and DR. HAROLD N. COLE JR.

Cutis Marmorata Congenita Unilateralis. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for the Department of Pediatrics, University Hospitals.

Case for Diagnosis: Acanthosis Nigricans Juvenilis? Presented by DR. HAROLD N. COLE, DR. J. R. DRIVER, and DR. HAROLD N. COLE JR.

George H. Curtis, M.D., *President*
John R. Haserick, M.D., *Secretary*
Harold N. Cole Jr., M.D., *Reporter*
Oct. 25, 1951

Lupus Erythematosus Disseminatus, Subacute. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. J. E. RAUSCHKOLB.

D. G., a white man aged 26 years, first noted an erythematous rash on his nose and cheeks one year ago. Sunlight aggravated this rash. His finger tips became tender and erythematous. Occasional dizzy spells were noted, with a sensation of "hot flashes." There were episodes of arthralgia in the wrists, ankles, knees, back, and neck. He later suffered from anorexia, weakness, and frequent abdominal cramps, with loose, foul-smelling stools. He lost 20 lb. (9.1 kg.) before his admission to City Hospital in June, 1951.

The patient's general health had been good prior to the onset of the present illness.

On physical examination, the temperature was 38 C. (100.4 F.), the pulse rate, 88, the respiration rate, 16, and the blood pressure, 128/83. There was an erythematous, slightly raised, moderately scaling eruption over the face, neck, including the V of the chest, the ears, and the backs of the hands. The conjunctivae were injected. There were some periorbital edema, and the lips were cracked and swollen. Physical examination otherwise gave essentially normal results.

Urinalysis disclosed a specific gravity of 1.019, a 3+ reaction for albumin, no reactions for sugar or acetone, and no formed elements. The hemogram revealed 14 gm. of hemoglobin per 100 cc. and 4,600,000 red blood cells and 2,600 white blood cells per cubic millimeter, with a differential count of 40% polymorphonuclear leucocytes, 38% lymphocytes, 6% monocytes, 7% eosinophiles, 2% unclassified cells, and 7% unsegmented cells. The sedimentation rate was 40 mm. per hour, corrected. The blood urea nitrogen was 10.9 mg.; sugar, 80 mg.; total proteins, 6.6 gm.; albumin, 4.0 gm., and globulin 2.6 gm., per 100 cc. Albumin-globulin ratio was 1.54. Serum chloride measured 102.6 mEq.; serum potassium, 3.1 mEq., and serum sodium, 139.0 mEq., per liter. A serologic test for syphilis was negative.

An L. E. cell test, as described by Dr. John R. Haserick (ARCH. DERMAT. & SYPH. **61**:889 [June] 1950), was negative. The L. E. test has been repeated, with negative results. Excretory urograms showed no pathological changes. Roentgenograms of the chest disclosed an essentially normal condition.

Histologic examination of a biopsy specimen of the skin of the neck showed thinning of the epidermis, with intraepithelial keratin plugging. Slight liquefaction degeneration of the basal layer was present. Lymphocytes and plasmacytes surrounded medium-sized and small vessels in the dermis. In one area adjacent to the epidermis were collections of lymphocytes, plasmacytes, and epithelial cells. There was slight basophilic degeneration of the collagen, but the elastic tissue was normal.

The patient received a course of cortisone therapy for 25 days. Initial improvement clinically was followed by a definite change for the worse. His serum globulin and albumin each fell to 2.2 gm. per 100 cc., ankle edema developed, and a definite gallop rhythm was heard over the precordium. He continued to excrete 6 to 8 gm. of albumin in his urine every 24 hours. Cortisone therapy was discontinued, and after 10 days he was given a course of corticotropin intramuscularly for 25 days. Corticotropin administration was then changed to the intravenous method, with some improvement. Efforts to replace his protein loss have included the administration of whole blood plasma and concentrated salt-free albumin, but the results on the whole have been disappointing. The chief problem here, which has characterized his entire hospital course, has been excessive renal loss of protein.

DISCUSSION

DR. E. W. NETHERTON: In view of the edema and heliotrope discoloration of the eyelids, the atrophy of the muscles confined to the shoulder girdle region, and the fact that the patient does not appear so acutely ill as one might expect in a case of acute disseminated lupus erythematosus, I favor a diagnosis of dermatomyositis.

DR. JOHN R. HASERICK: I think that the cortisone therapy has changed the picture a great deal. I should like to support Dr. Netherton in the diagnosis of dermatomyositis. It is true that the patient has an albuminuria, and it is true that he has a leucopenia. The skin manifestations are certainly acceptable as lupus erythematosus. However, he has many of the manifestations of dermatomyositis. He has the wasting of the shoulder girdle muscles, with the still-intact muscles of the lower extremities. He has had a very poor response to steroid therapy, which is characteristic of dermatomyositis, whereas lupus erythematosus usually shows some response. The heliotrope eyelids which Dr. Netherton mentioned were to me rather striking in this man. He does not have the cigaret-paper thinness of the knuckles which is supposed to be characteristic of dermatomyositis. I suggest that a muscle biopsy be done on this man, the specimen to be taken from the pectoralis muscle rather than from the gastrocnemius group.

DR. E. S. HALLINGER: I agree with Dr. Netherton in the diagnosis of dermatomyositis, in view of the fact that the patient told me that he had had an acute streptococcic sore throat six months previous to the onset of his symptoms, at which time he was very sick and was given penicillin injections. He also told me that these cutaneous symptoms, the erythematous lesions on the hands, face, and neck, preceded the present muscular weakness. He also has a periorbital edema, which would go with that diagnosis. I suggest a trial of tocopherols on that basis and in view of the fact that the present treatment has not seemed to alleviate any of his symptoms.

DR. J. E. RAUSCHKOLB: We have followed this man for the last six months. He was sent in to us with manifestations which have changed considerably to bring about the present picture. He came in with the typical butterfly type of distribution over the face, with the typical erythematous bases of the nails, with the leucopenia, with a white blood cell count varying from 2,000 to 5,000, with the reversible albumin-globulin ratio, and with a fever, being very sick. He had also, from the laboratory findings, a nephrosis or nephritis in which he was excreting red cells with a tremendous amount of albumin; this helped to produce the reversal of the albumin-globulin ratio. At that time, because of the duration of the process before he came in, we made the diagnosis of an acute lupus erythematosus, perhaps of the disseminated type, because he had the eruption on his chest, face, and neck. At the time he came in, the periorbital edema was not present. We did bone marrow studies and L. E. studies and were never able to find a positive L. E. picture in the bone marrow or in the peripheral blood. We sent a specimen to Dr. Haserick, who reported a negative plasma L. E. test. We thought that this was an extreme case, interesting and unusual, of subacute disseminated lupus erythematosus in a young man. Because we did not have cortisone at that time, we gave him tocopherols and bismuth, with no improvement. When we gave him cortisone, he had a reversal of the critical symptoms and signs almost immediately, and he improved considerably. Later his condition became worse, and he did not respond to increased doses of cortisone. He continued to excrete albumin in the urine. He presented such a problem from the medical standpoint that we thought it advisable to transfer him to the Medical Service, where he remains.

Up to now the picture has not changed too much. We did consider a diagnosis of dermatomyositis, but the over-all picture was one of a subacute disseminated lupus erythematosus, which is a little unusual in the male. If the patient were a female, she would have been dead by this time or she would have reacted very favorably to the cortisone.

Case for Diagnosis: Parapsoriasis en Plaques? Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. J. E. RAUSCHKOLB.

M. S., a 33-year-old Negro woman, first noted the onset of a mildly pruritic rash in April, 1951, starting with a small area on the left arm and later spreading over the body in a patchy distribution. The only drugs or medicines taken by the patient prior to the onset of the rash was magnesium citrate occasionally.

The patient has no history of allergy or previous skin disorders. She does housework. Systemic review gave an essentially normal picture.

There is a follicular papulosquamous eruption of the trunk and extremities, with peripheral scaling and central hyperpigmentation. Some of the lesions are confluent and form plaques, especially over the extensor surfaces of the extremities. The results of the remainder of the physical examination were essentially normal.

Urinalysis and a hemogram revealed no abnormalities. Total serum proteins were 8.0 gm. per 100 cc., with 5 gm. of albumin and 3 gm. of globulin, and an albumin-globulin ratio of 1.67. Blood Kline and Wassermann reactions were negative. Roentgenologic examination of the heart, lungs, and hands revealed no abnormalities.

Histologic examination of a skin biopsy specimen from the back showed some acanthosis and spongiosis. There was no hyperkeratosis or parakeratosis present. The rete pegs were regular and normal in size. In the dermis there were focal accumulations of leucocytes, macrophages, and lymphocytes around the blood vessels.

DISCUSSION

DR. H. N. COLE: A drug eruption would have to be considered. I questioned this patient very closely and could get no history of the ingestion of drugs. On examination of the lesions some of the areas show a somewhat lichenoid appearance, but the patient gives no history of pruritus. The lesions seem to be quiescent as far as disturbing the patient is concerned and remain about the same. I am inclined to think that this is parapsoriasis en plaques.

DR. G. A. DE OREO: I entertained the possibility that this might be an acuminate type of tuberculid. Another biopsy specimen should be taken from one of the papular lesions.

DR. H. N. COLE: We used to see a great deal of lichen scrofulosus. The picture remains for only a few days or a week at the most, and then it disappears. Then there will be another shower, and the picture will recur. This patient has had these lesions for a long time; therefore, her condition is not compatible with the ordinary picture of lichen scrofulosus.

Lichen Planopilaris of Pringle. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. J. E. RAUSCHKOLB.

H. M., a white woman aged 51, noted progressive loss of hair during the past eight years and a generalized pruritic papular eruption since December, 1950.

Eight years ago the patient first noted an area of scanty hair growth over the occiput. This area enlarged slowly until three years ago, when a diffuse, ragged alopecia developed. In December, 1950, a sparse, flat, papular, moderately pruritic eruption appeared in the axillae, under the breasts, and in the groins, with some involvement over the trunk and extremities.

The scalp shows a diffuse patchy alopecia. No atrophy or scarring is seen. There are scattered flat, reddish papules, 0.3 to 0.8 cm. in diameter, particularly in the occipital region. There is a 1.5-cm. plaque, containing discrete reddish papules, in a follicular distribution on the dorsum of the right wrist. Other small papules may be seen on the extremities. The buccal mucosa exhibits a slightly raised, gray reticulum and a mottled erythema. Grouped hyperpigmented macules may be seen in the axillae.

Results of urinalysis were normal. The hemogram revealed 12.0 gm. of hemoglobin per 100 cc. and 3,500,000 red blood cells and 5,000 white blood cells per cubic millimeter, with 60% polymorphonuclear leucocytes, 37% lymphocytes, and 3% monocytes. Serum cholesterol was 286 mg. and cholesterol esters 194 mg. per 100 cc. Blood Wassermann and Kline reactions were negative. Roentgenograms of the lungs and heart showed no abnormalities. The basal metabolic rate was + 2%.

The report on a histologic examination of a skin biopsy specimen was as follows:

"Section of skin of forearm reveals a portion of the skin with moderate hyperkeratosis. There is slight thickening of the granular layer in areas. There is degeneration of the basal layer, with areas of vacuolation. One rete peg is saw-toothed. There is moderate lymphocytic infiltration in the upper corium. There are other areas showing acanthosis. Section of the scalp is essentially similar to that of the skin of the forearm, but in addition a hair follicle containing keratotic plugs and perifollicular lymphocytic infiltration is seen."

DISCUSSION

DR. H. N. COLE: Recently, in our office we saw a patient who had this condition, with lesions on the arms and upper part of the trunk. There were sharply defined areas of alopecia. Examination also revealed lesions on the trunk and extremities. I was very much interested in the patient shown today.

DR. G. A. DE OREO: I think it is fairly well accepted now that this condition is a single entity, namely, lichen planus with involvement of the hair follicles of the body and scalp, of the glabrous skin as we see in lichen planus, and of the mucous membranes. It is interesting that, when Dr. Pringle wrote his monograph on lichen spinulosus et folliculitis decalvans in 1921, he thought he was seeing two distinct entities. Not until a few years later did he finally recognize that lichen spinulosus was not the correct diagnosis. In spite of that, you will find that the textbook authors have apparently forgotten to revise the chapters they copied from their predecessors, for they continue to call this condition lichen spinulosus et folliculitis decalvans. However, this patient has unmistakable lichen planus; consequently, I think lichen spinulosus et folliculitis decalvans is merely lichen planus with different types of manifestations. In the microscopic section it can be seen that the falling-out of the hair is due to the banal type of thickening which presses against the hair follicle, so that the blood supply is disturbed and the hair falls out. The process may be reversible. Many times the hair grows back, but for this patient, who has had the condition for nearly a year, the chances of regrowing hair are very slight. She has this condition also in her axillae. The glabrous skin lesions have improved considerably. She has had half a dozen bismuth injections. She shows the Koebner phenomenon in scratch marks on the wrists and forearms.

Mycosis Fungoides with Transition to Hodgkin's Granuloma. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. J. E. RAUSCHKOLB.

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Case for Diagnosis: Granuloma Annulare? Presented by DR. E. H. JONES, WARREN, and DR. E. H. JONES JR.

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Acrodermatitis Chronica Atrophicans. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. J. E. RAUSCHKOLB.

News and Comment

ANNOUNCEMENTS

Meeting of the Pacific Dermatologic Association.—The Pacific Dermatologic Association will hold its annual meeting at the Palace Hotel in San Francisco, Aug. 29 to 31, 1952. The guest speaker will be Dr. Marcus R. Caro, of Chicago. This year's program is under the chairmanship of Dr. Nelson Paul Anderson, of Los Angeles. Among the features will be a demonstration of the treponome-immobilization test, reports on research activities of the member universities, a clinical and histopathologic meeting, and a discussion of dermatologic economics.

CORRECTIONS

The following corrections should be made in the Directory of Dermatologic Societies which appeared in the July issue, page 141:

The Northern New Jersey Dermatological Society has changed its name to the New Jersey Dermatological Society. Its president is Eva T. Brodkin, Newark, N. J., and its secretary is Frederick C. Licks, 64 Scotland Rd., South Orange, N. J.

The president of the Rocky Mountain Dermatological Society is Gerald M. Frumess, 2200 E. 18th Ave., Denver, and the Secretary is Thomas W. Moffatt, 822 Majestic Bldg., Denver.

Books

The Hair and Scalp. By Agnes Savill. Fourth edition. Price, 25 shillings net. Pp. 316, with illustrations. Edward Arnold & Co., 41-43 Maddox St., London, W.1, 1951.

The author, who was a pupil of Sabouraud, has had exceptionally wide experience with problems concerning the hair and scalp. In this interesting small volume, she expresses many of her own opinions and conclusions and, in addition, contributes a very adequate number of references from the classical and recent literature.

For a volume of its size, a remarkable amount of information is available: the macroscopic descriptions are detailed and accurate, but, unfortunately, the corresponding histopathologic discussions are often too brief. The book contains 59 photographs which are clear and excellent; it would, however, benefit by an increase in the number of photomicrographs of the scalp in this day of confirmation of clinical impressions by histopathologic examinations.

The author is keenly aware of the relation of internal diseases to the state of health of the hair and scalp and in her practice resorts to supplementary therapy with thyroid and other hormonal agents. In certain cases, however, the scientific background to support the rationale of this type of therapy is rather inadequately discussed. The many methods of treatment may leave the reader somewhat confused, and a word of caution is timely to those who would follow it overenthusiastically.

There may be some question of the value of the elaborate and long-drawn-out methods of therapy for the usual types of baldness, which are written of in a very complete and interesting manner. The chapter on hirsutism is a new and welcome addition to this edition of the book.

The detailed discussion of the historical and practical aspects of cosmetics used on the hair, particularly dyes and their possibly harmful effects, is well done. The arguments presented are expressed in simple language which would be well understood by the public.

For those interested in the study, practical diagnosis, and treatment of various hair and scalp lesions, this book offers a useful and practical aid, and its presentation provides very pleasant reading.

Syphilis. By Richard S. Weiss, M.D., Dermatologist-in-Chief, Barnard Free Skin and Cancer Hospital, St. Louis, and Herbert L. Joseph, M.D., Consultant in Dermatology and Syphilology, United States Air Force Base, Travis Air Force Base, California. Price, $5. Pp. 180, with 42 illustrations. Thos. Nelson & Sons, 385 Madison Ave., New York 17 [medical book-publishing business purchased by Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2], 1951.

Weiss and Joseph have written a short book on syphilis, but it contains most of the essential features of the disease. The book is not cluttered with references but gives the essential or significant references in each chapter. The concise and brief descriptions and the detailed treatment systems will be readily accepted by the general practitioner and the medical student. Some of the photographs are not clear and lack detail; otherwise the book is recommended as a valuable aid to the practitioner who occasionally encounters the problems offered by the patient with syphilis.

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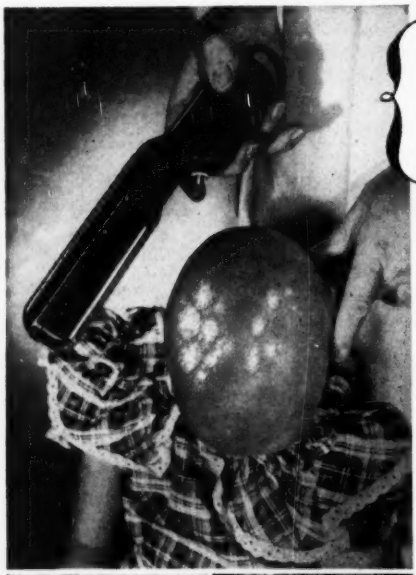

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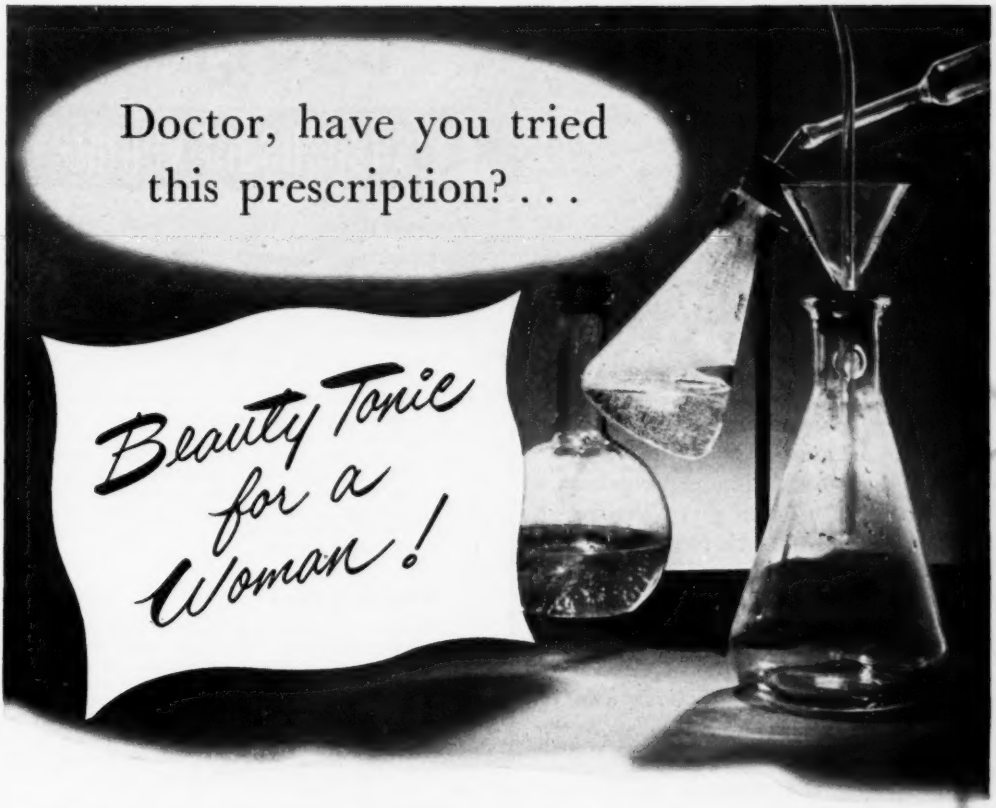

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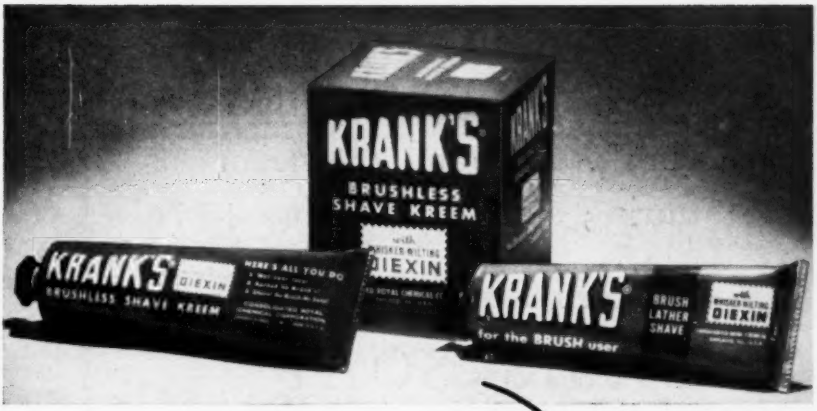

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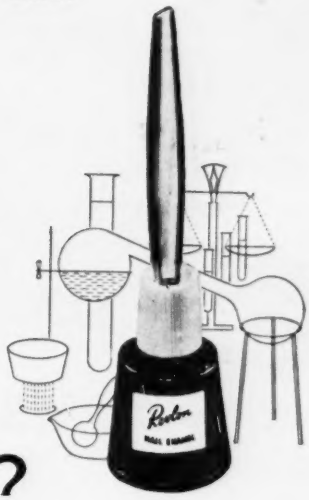

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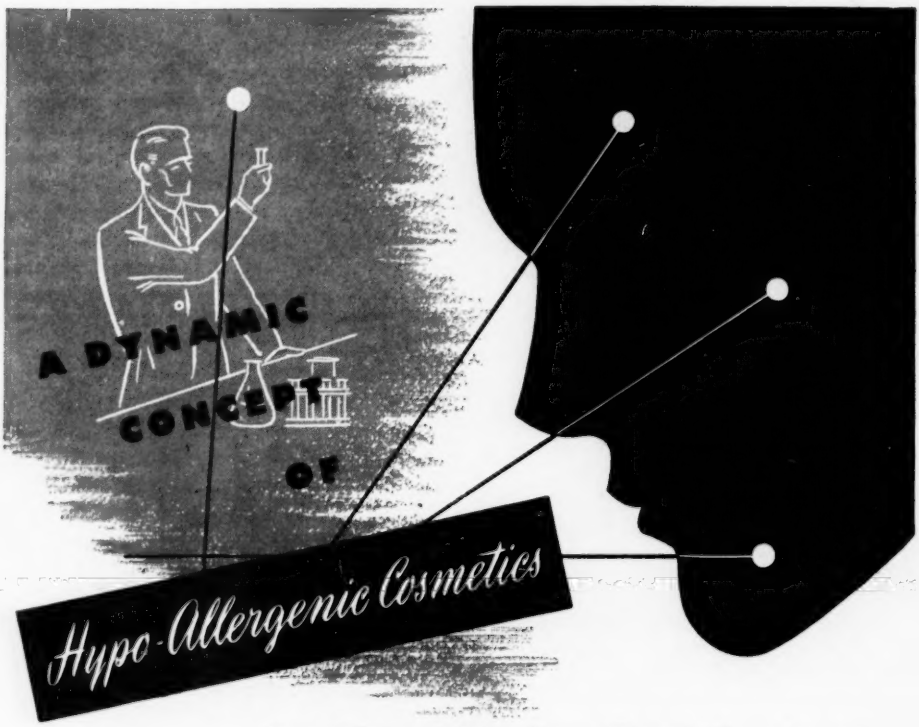

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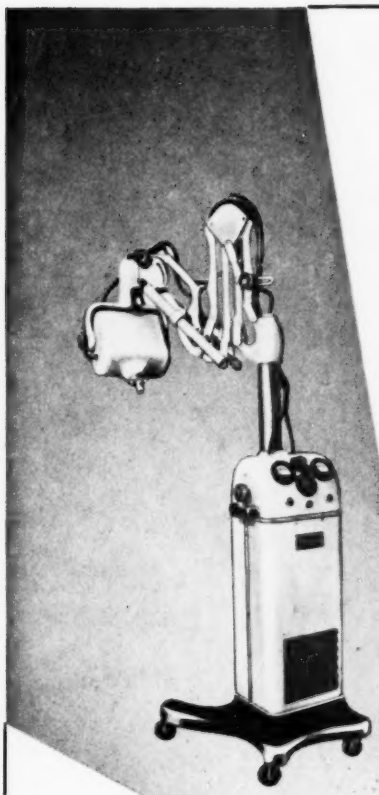

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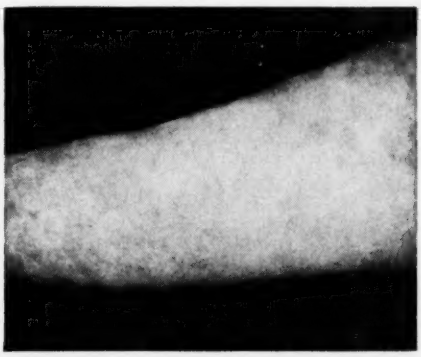

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